

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
10 October 2002 (10.10.2002)

PCT

(10) International Publication Number
WO 02/079197 A1

(51) International Patent Classification⁷: C07D 405/04, A61K 31/506, C07D 239/42, 213/74, A61K 31/4418, A61P 25/00, 37/00, 9/00, 29/00, C07D 417/04, 403/04

(74) Agents: ROBIDOUX, Andrea et al.; Vertex Pharmaceuticals Inc., 130 Waverly Street, Cambridge, MA 02139-4242 (US).

(21) International Application Number: PCT/US02/09554

(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(22) International Filing Date: 28 March 2002 (28.03.2002)

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

(25) Filing Language: English

English

(26) Publication Language: English

English

(30) Priority Data:
60/279,961 29 March 2001 (29.03.2001) US

Published:

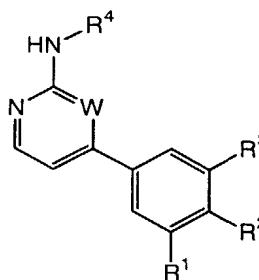
— with international search report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

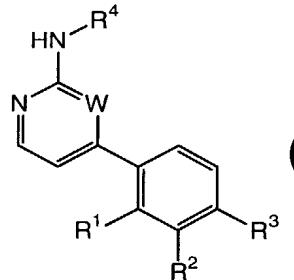
(72) Inventors; and

(75) Inventors/Applicants (for US only): **BETHIEL, Randy** [US/US]; 314 Massachusetts Avenue, Lexington, MA 02420 (US). **COCHRAN, John** [US/US]; 24 Royal Crest Drive #3, North Andover, MA 01845 (US). **MOON, Young-Choon** [KR/US]; 1 Great Rock Road, Lexington, MA 02421 (US). **NANTHAKUMAR, Susanthini** [LK/US]; 253 Spiers Road, Newton, MA 02459 (US).

(54) Title: INHIBITORS OF C-JUN N-TERMINAL KINASES (JNK) AND OTHER PROTEIN KINASES



(I)



(II)

(57) Abstract: The present invention provide a compound of formula I or II:or a pharmaceutically acceptable derivative thereof, wherein R₁, R₂, R₃, and R₄ are as described in the specification. These compounds are inhibitors of protein kinase, particularly inhibitors of JNK, a mammalian proteinkinase involved cell proliferation, cell death and response to extracellular stimuli; and Src-family kinases, especially Src and Lck kinases.

WO 02/079197 A1

These compounds are also inhibitors of GSK3 and CDK2 kinases. The invention also relates to methods for producing these inhibitors. The invention also provides pharmaceutical compositions comprising the inhibitors of the invention and methods of utilizing those compositions in the treatment and prevention of various disorders.

INHIBITORS OF c-JUN N-TERMINAL KINASES (JNK) AND OTHER
PROTEIN KINASES

CROSS REFERENCE TO RELATED APPLICATION

This application claims priority to US Provisional Patent Application 60/279,961 filed March 29, 2001, the contents of which is incorporated herein by reference.

TECHNICAL FIELD OF INVENTION

The present invention relates to inhibitors of 5 protein kinase, especially c-Jun N-terminal kinases (JNK) and Src-family of kinases, which are members of the mitogen-activated protein (MAP) kinase family. There are a number of different genes and isoforms which encode JNKs. Members of the JNK family regulate signal 10 transduction in response to environmental stress and proinflammatory cytokines and have been implicated in the mediation of a number of different disorders. Members of the Src family are implicated in a number of human diseases. The invention also relates to inhibitors of 15 GSK3 kinase, which is implicated in diabetes and other disorders, and CDK2 kinase which plays a role in the regulation of the cell division cycle. The invention also provides pharmaceutical compositions comprising the inhibitors of the invention and methods of utilizing 20 those compositions in the treatment and prevention of various disorders.

-2-

BACKGROUND OF THE INVENTION

Mammalian cells respond to extracellular stimuli by activating signaling cascades that are mediated by members of the mitogen-activated protein (MAP) kinase family, which include the extracellular signal regulated kinases (ERKs), the p38 MAP kinases and the c-Jun N-terminal kinases (JNKs). MAP kinases (MAPKs) are activated by a variety of signals including growth factors, cytokines, UV radiation, and stress-inducing agents. MAPKs are serine/threonine kinases and their activation occurs by dual phosphorylation of threonine and tyrosine at the Thr-X-Tyr segment in the activation loop. MAPKs phosphorylate various substrates including transcription factors, which in turn regulate the expression of specific sets of genes and thus mediate a specific response to the stimulus.

In the c-Jun NH₂-terminal protein kinases, also known as JNKs, three distinct genes, JNK1, JNK2, JNK3 have been identified and at least ten different splicing isoforms of JNKs exist in mammalian cells [Gupta et al., EMBO J., 15:2760-70 (1996)]. Members of the JNK family are activated by proinflammatory cytokines, such as tumor necrosis factor- α (TNF α) and interleukin-1 β (IL-1 β), as well as by environmental stress, including anisomycin, UV irradiation, hypoxia, and osmotic shock [Minden et al., Biochimica et Biophysica Acta, 1333:F85-F104 (1997)].

The down-stream substrates of JNKs include transcription factors c-Jun, ATF-2, Elk1, p53 and a cell death domain protein (DENN) [Zhang et al. Proc. Natl. Acad. Sci. USA, 95:2586-91 (1998)]. Each JNK isoform binds to these substrates with different affinities, suggesting a regulation of signaling pathways by

-3-

substrate specificity of different JNKs *in vivo* (Gupta et al., *supra*).

JNKs, along with other MAPKs, have been implicated in the mediation of cellular response to 5 cancer, thrombin-induced platelet aggregation, immunodeficiency disorders, autoimmune diseases, cell death, allergies, osteoporosis and heart disease. The therapeutic conditions related to activation of the JNK pathway include chronic myelogenous leukemia (CML), 10 rheumatoid arthritis, asthma, osteoarthritis, ischemia, cancer and neurodegenerative diseases.

Several reports have detailed the importance of JNK activation associated with liver disease or episodes of hepatic ischemia [Nat. Genet. 21:326-9 (1999); FEBS Lett. 420:201-4 (1997); J. Clin. Invest. 102:1942-50 15 (1998); Hepatology 28:1022-30 (1998)].

A role for JNK in cardiovascular disease such as myocardial infarction or congestive heart failure has also been reported as it has been shown JNK mediates 20 hypertrophic responses to various forms of cardiac stress [Circ. Res. 83:167-78 (1998); Circulation 97:1731-7 (1998); J. Biol. Chem. 272:28050-6 (1997); Circ. Res. 79:162-73 (1996); Circ. Res. 78:947-53 (1996); J. Clin. Invest. 97:508-14 (1996)].

25 It has been demonstrated that the JNK cascade also plays a role in T-cell activation, including activation of the IL-2 promoter. Thus, inhibitors of JNK have potential therapeutic value in altering pathologic immune responses [J. Immunol. 162:3176-87 (1999); Eur. J. Immunol. 28:3867-77 (1998); J. Exp. Med. 186:941-53 30 (1997); Eur. J. Immunol. 26:989-94 (1996)].

A role for JNK activation in various cancers has also been established, suggesting the potential use

-4-

of JNK inhibitors in cancer. For example, constitutively activated JNK is associated with HTLV-1 mediated tumorigenesis [Oncogene 13:135-42 (1996)]. The proliferative effects of bFGF and OSM on Kaposi's sarcoma (KS) cells are mediated by their activation of the JNK signaling pathway [J. Clin. Invest. 99:1798-804 (1997)]. Other proliferative effects of other cytokines implicated in KS proliferation, such as vascular endothelial growth factor (VEGF), IL-6 and TNF α , are also mediated by JNK.

In addition, regulation of the c-jun gene in p210 BCR-ABL transformed cells corresponds with activity of JNK, suggesting a role for JNK inhibitors in the treatment for chronic myelogenous leukemia (CML) [Blood 92:2450-60 (1998)].

JNK1 and JNK2 are widely expressed in a variety of tissues. In contrast, JNK3, is selectively expressed in the brain and to a lesser extent in the heart and testis [Gupta et al., *supra*; Mohit et al., Neuron 14:67-78 (1995); Martin et al., Brain Res. Mol. Brain Res. 35:47-57 (1996)]. JNK3 has been linked to neuronal apoptosis induced by kainic acid, indicating a role of JNK in the pathogenesis of glutamate neurotoxicity. In the adult human brain, JNK3 expression is localized to a subpopulation of pyramidal neurons in the CA1, CA4 and subiculum regions of the hippocampus and layers 3 and 5 of the neocortex [Mohit et al., *supra*]. The CA1 neurons of patients with acute hypoxia showed strong nuclear JNK3-immunoreactivity compared to minimal, diffuse cytoplasmic staining of the hippocampal neurons from brain tissues of normal patients [Zhang et al., *supra*]. Thus, JNK3 appears to be involved in hypoxic and ischemic damage of CA1 neurons in the hippocampus.

-5-

In addition, JNK3 co-localizes immunocytochemically with neurons vulnerable in Alzheimer's disease [Mohit et al., *supra*]. Disruption of the JNK3 gene caused resistance of mice to the excitotoxic glutamate receptor agonist kainic acid, including the effects on seizure activity, AP-1 transcriptional activity and apoptosis of hippocampal neurons, indicating that the JNK3 signaling pathway is a critical component in the pathogenesis of glutamate neurotoxicity (Yang et al., *Nature*, 389:865-870 (1997)].

Based on these findings, JNK signaling, especially that of JNK3, has been implicated in the areas of apoptosis-driven neurodegenerative diseases such as Alzheimer's Disease, Parkinson's Disease, ALS (Amyotrophic Lateral Sclerosis), epilepsy and seizures, Huntington's Disease, traumatic brain injuries, as well as ischemic and hemorrhaging stroke.

There is a high unmet medical need to develop JNK specific inhibitors that are useful in treating the various conditions associated with JNK activation, especially considering the currently available, relatively inadequate treatment options for the majority of these conditions.

The Src-family of kinases are implicated in cancer, immune system dysfunction, and bone remodeling diseases. For general reviews, see Thomas and Brugge, *Annu. Rev. Cell Dev. Biol.* (1997) 13, 513; Lawrence and Niu, *Pharmacol. Ther.* (1998) 77, 81; Tatosyan and Mizenina, *Biochemistry (Moscow)* (2000) 65, 49; Boschelli et al., *Drugs of the Future* 2000, 25(7), 717, (2000).

Members of the Src family include the following eight kinases in mammals: Src, Fyn, Yes, Fgr, Lyn, Hck, Lck, Blk and Yrc. These are nonreceptor protein kinases

- 6 -

that range in molecular mass from 52 to 62 kD. All are characterized by a common structural organization that is comprised of six distinct functional domains: Src homology domain 4 (SH4), a unique domain, SH3 domain, SH2 domain, a catalytic domain (SH1), and a C-terminal regulatory region. Tatosyan et al. *Biochemistry (Moscow)* 65, 49-58 (2000).

Based on published studies, Src kinases are considered as potential therapeutic targets for various human diseases. Mice that are deficient in Src develop osteopetrosis, or bone build-up, because of depressed bone resorption by osteoclasts. This suggests that osteoporosis resulting from abnormally high bone resorption can be treated by inhibiting Src. Soriano et al., *Cell*, 69, 551 (1992) and Soriano et al., *Cell*, 64, 693 (1991).

Suppression of arthritic bone destruction has been achieved by the overexpression of CSK in rheumatoid synoviocytes and osteoclasts. Takayanagi et al., *J. Clin. Invest.*, 104, 137 (1999). CSK, or C-terminal Src kinase, phosphorylates and thereby inhibits Src catalytic activity. This implies that Src inhibition may prevent joint destruction that is characteristic in patients suffering from rheumatoid arthritis. Boschelli et al., *Drugs of the Future* 2000, 25(7), 717, (2000).

Src also plays a role in the replication of hepatitis B virus. The virally encoded transcription factor HBx activates Src in a step required for propagation of the virus. Klein et al., *EMBO J.*, 18, 5019, (1999) and Klein et al., *Mol. Cell. Biol.*, 17, 6427 (1997).

A number of studies have linked Src expression to cancers such as colon, breast, hepatic and pancreatic

- 7 -

cancer, certain B-cell leukemias and lymphomas.

Talamonti et al., *J. Clin. Invest.*, 91, 53 (1993); Lutz et al., *Biochem. Biophys. Res.* 243, 503 (1998); Rosen et al., *J. Biol. Chem.*, 261, 13754 (1986); Bolen et al.,

5 *Proc. Natl. Acad. Sci. USA*, 84, 2251 (1987); Masaki et al., *Hepatology*, 27, 1257 (1998); Biscardi et al., *Adv. Cancer Res.*, 76, 61 (1999); Lynch et al., *Leukemia*, 7, 1416 (1993); Furthermore, antisense Src expressed in ovarian and colon tumor cells has been shown to inhibit
10 tumor growth. Wiener et al., *Clin. Cancer Res.*, 5, 2164 (1999); Staley et al., *Cell Growth Diff.*, 8, 269 (1997).

Other Src family kinases are also potential therapeutic targets. Lck plays a role in T-cell signaling. Mice that lack the Lck gene have a poor ability to develop thymocytes. The function of Lck as a positive activator of T-cell signaling suggests that Lck inhibitors may be useful for treating autoimmune disease such as rheumatoid arthritis. Molina et al., *Nature*, 357, 161 (1992). Hck, Fgr and Lyn have been identified
15 as important mediators of integrin signaling in myeloid leukocytes. Lowell et al., *J. Leukoc. Biol.*, 65, 313 (1999). Inhibition of these kinase mediators may therefore be useful for treating inflammation. Boschelli et al., *Drugs of the Future* 2000, 25(7), 717, (2000).

25 Glycogen synthase kinase-3 (GSK-3) is a serine/threonine protein kinase comprised of α and β isoforms that are each encoded by distinct genes [Coghlan et al., *Chemistry & Biology*, 7, 793-803 (2000); Kim and Kimmel, *Curr. Opinion Genetics Dev.*, 10, 508-514 (2000)].
30 GSK-3 has been implicated in various diseases including diabetes, Alzheimer's disease, CNS disorders such as manic depressive disorder and neurodegenerative diseases, and cardiomyocyte hypertrophy [WO 99/65897; WO 00/38675;

- 8 -

and Haq *et al.*, *J. Cell Biol.* (2000) 151, 117]. These diseases may be caused by, or result in, the abnormal operation of certain cell signaling pathways in which GSK-3 plays a role. GSK-3 has been found to
5 phosphorylate and modulate the activity of a number of regulatory proteins. These include glycogen synthase which is the rate limiting enzyme necessary for glycogen synthesis, the microtubule associated protein Tau, the gene transcription factor β -catenin, the translation
10 initiation factor eIF2B, as well as ATP citrate lyase, axin, heat shock factor-1, c-Jun, c-Myc, c-Myb, CREB, and CEPB α . These diverse targets implicate GSK-3 in many aspects of cellular metabolism, proliferation, differentiation and development.

15 In a GSK-3 mediated pathway that is relevant for the treatment of type II diabetes, insulin-induced signaling leads to cellular glucose uptake and glycogen synthesis. Along this pathway, GSK-3 is a negative regulator of the insulin-induced signal. Normally, the
20 presence of insulin causes inhibition of GSK-3 mediated phosphorylation and deactivation of glycogen synthase. The inhibition of GSK-3 leads to increased glycogen synthesis and glucose uptake [Klein *et al.*, *PNAS*, 93, 8455-9 (1996); Cross *et al.*, *Biochem. J.*, 303, 21-26 (1994); Cohen, *Biochem. Soc. Trans.*, 21, 555-567 (1993);
25 Massillon *et al.*, *Biochem J.* 299, 123-128 (1994)]. However, in a diabetic patient where the insulin response is impaired, glycogen synthesis and glucose uptake fail to increase despite the presence of relatively high blood
30 levels of insulin. This leads to abnormally high blood levels of glucose with acute and long term effects that may ultimately result in cardiovascular disease, renal failure and blindness. In such patients, the normal

-9-

insulin-induced inhibition of GSK-3 fails to occur. It has also been reported that in patients with type II diabetes, GSK-3 is overexpressed [WO 00/38675]. Therapeutic inhibitors of GSK-3 are therefore potentially 5 useful for treating diabetic patients suffering from an impaired response to insulin.

GSK-3 activity has also been associated with Alzheimer's disease. This disease is characterized by the well-known β -amyloid peptide and the formation of 10 intracellular neurofibrillary tangles. The neurofibrillary tangles contain hyperphosphorylated Tau protein where Tau is phosphorylated on abnormal sites. GSK-3 has been shown to phosphorylate these abnormal sites in cell and animal models. Furthermore, inhibition 15 of GSK-3 has been shown to prevent hyperphosphorylation of Tau in cells [Lovestone et al., *Current Biology* 4, 1077-86 (1994); Brownlees et al., *Neuroreport* 8, 3251-55 (1997)]. Therefore, it is believed that GSK-3 activity may promote generation of the neurofibrillary tangles and 20 the progression of Alzheimer's disease.

Another substrate of GSK-3 is β -catenin which is degraded after phosphorylation by GSK-3. Reduced levels of β -catenin have been reported in schizophrenic patients and have also been associated with other 25 diseases related to increase in neuronal cell death [Zhong et al., *Nature*, 395, 698-702 (1998); Takashima et al., *PNAS*, 90, 7789-93 (1993); Pei et al., *J. Neuropathol. Exp.*, 56, 70-78 (1997)].

Cyclin-dependent kinases (CDKs) are 30 serine/threonine protein kinases consisting of a β -sheet rich amino-terminal lobe and a larger carboxy-terminal lobe which is largely α -helical. The CDKs display the 11

-10-

subdomains shared by all protein kinases and range in molecular mass from 33 to 44 kD. This family of kinases, which includes CDK1, CKD2, CDK4, and CDK6, requires phosphorylation at the residue corresponding to CDK2

- 5 Thr160 in order to be fully active [Meijer, L., *Drug Resistance Updates*, 3, 83-88 (2000)].

Each CDK complex is formed from a regulatory cyclin subunit (e.g., cyclin A, B1, B2, D1, D2, D3, and E) and a catalytic kinase subunit (e.g., CDK1, CDK2, 10 CDK4, CDK5, and CDK6). Each different kinase/cyclin pair functions to regulate the different and specific phases of the cell cycle known as the G₁, S, G₂, and M phases [Nigg, E., *Nature Reviews*, 2, 21-32 (2001); Flatt, P., Pietenpol, J., *Drug Metabolism Reviews*, 32, 283-305 15 (2000)].

The CDKs have been implicated in cell proliferation disorders, particularly in cancer. Cell proliferation is a result of the direct or indirect deregulation of the cell division cycle and the CDKs play 20 a critical role in the regulation of the various phases of this cycle. For example, the over-expression of cyclin D1 is commonly associated with numerous human cancers including breast, colon, hepatocellular carcinomas and gliomas [Flatt, P., Pietenpol, J., *Drug 25 Metabolism Reviews*, 32, 283-305 (2000)]. The CDK2/cyclin E complex plays a key role in the progression from the early G₁ to S phases of the cell cycle and the overexpression of cyclin E has been associated with various solid tumors. Therefore, inhibitors of cyclins 30 D1, E, or their associated CDKs are useful targets for cancer therapy [Kaubisch, A., Schwartz, G., *The Cancer Journal*, 6, 192-212 (2000)].

-11-

CDKs, especially CDK2, also play a role in apoptosis and T-cell development. CDK2 has been identified as a key regulator of thymocyte apoptosis [Williams, O., et al, *European Journal of Immunology*, 5 709-713 (2000)]. Stimulation of CDK2 kinase activity is associated with the progression of apoptosis in thymocytes, in response to specific stimuli. Inhibition of CDK2 kinase activity blocks this apoptosis resulting in the protection of thymocytes.

10 In addition to regulating the cell cycle and apoptosis, the CDKs are directly involved in the process of transcription. Numerous viruses require CDKs for their replication process. Examples where CDK inhibitors restrain viral replication include human cytomegakovirus, 15 herpes virus, and varicella-zoster virus [Meijer, L., *Drug Resistance Updates*, 3, 83-88 (2000)].

Inhibition of CDK is also useful for the treatment of neurodegenerative disorders such as Alzheimer's disease. The appearance of Paired Helical 20 Filaments (PHF), associated with Alzheimer's disease, is caused by the hyperphosphorylation of Tau protein by CDK5/p25 [Meijer, L., *Drug Resistance Updates*, 3, 83-88 (2000)].

As a result of the biological importance of 25 protein kinases, there is current interest in therapeutically effective protein kinase inhibitors. Certain aryl substituted 2-aminopyrimidines are known as protein kinase inhibitors. See [United States patents 5,958,935, 5,863,924, 5,612,340, and PCT publication WO 30 01/29009].

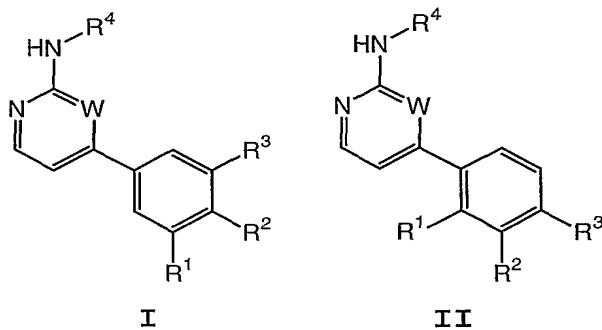
Accordingly, there is still a great need to develop potent inhibitors of JNKs and Src family kinases, including JNK3, Src, and Lck inhibitors, and of GSK3 and

-12-

CDK2 inhibitors that are useful in treating various diseases or conditions associated with JNK3, Src, Lck, GSK3, and CDK2 activation.

SUMMARY OF THE INVENTION

5 It has now been found that compounds of this invention and pharmaceutical compositions thereof are effective as inhibitors of c-Jun N-terminal kinases (JNK), Src, Lck, GSK3, and CDK2. These compounds have the general formulae I and II:



10

I

II

or a pharmaceutically acceptable derivative thereof, wherein W is nitrogen or CH and R¹, R², R³, and R⁴ are as described below.

15 These compounds and pharmaceutical compositions thereof are useful for treating or preventing a variety of disorders, such as heart disease, diabetes, Alzheimer's disease, immunodeficiency disorders, inflammatory diseases, allergic diseases, autoimmune diseases, destructive bone disorders such as osteoporosis, proliferative disorders, infectious diseases and viral diseases. The compositions are also useful in methods for preventing cell death and hyperplasia and therefore may be used to treat or prevent reperfusion/ischemia in stroke, heart attacks, and organ hypoxia. The compositions are also useful in methods for preventing thrombin-induced platelet aggregation. The

20

25

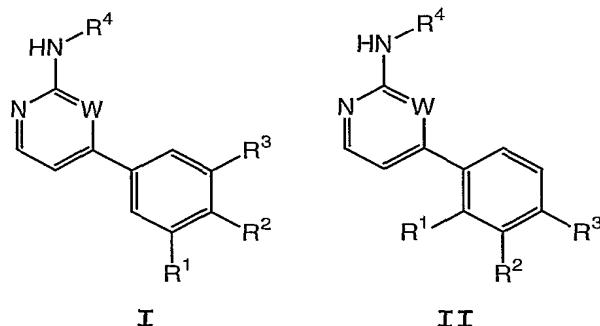
-13-

compositions are especially useful for disorders such as chronic myelogenous leukemia (CML), rheumatoid arthritis, asthma, osteoarthritis, ischemia, cancer, liver disease including hepatic ischemia, heart disease such as

- 5 myocardial infarction and congestive heart failure, pathologic immune conditions involving T cell activation and neurodegenerative disorders.

DETAILED DESCRIPTION OF THE INVENTION

10 The present invention relates to a compound of formula I or II:



or a pharmaceutically acceptable derivative thereof,

15 wherein:

each W is independently selected from nitrogen or CH;

each R¹, R², and R³ is independently selected from

halogen, QR, Q_(n)CN, Q_(n)NO₂, or Q_(n)Ar²; wherein:

R¹ and R² or R² and R³ are optionally taken together to form a 4-8 membered saturated, partially unsaturated, or fully unsaturated ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

n is zero or one;

Q is a C₁₋₄ alkylidene chain wherein one methylene unit of

Q is optionally replaced by O, S, NR, NRCO, NRCONR,

NRCO₂, CO, CO₂, CONR, OC(O)NR, SO₂, SO₂NR, NRSO₂,

NRSO₂NR, C(O)C(O), or C(O)CH₂C(O);

-14-

each R is independently selected from hydrogen or an optionally substituted C₁-C₄ aliphatic, wherein:

two R bound to the same nitrogen atom are optionally taken together with the nitrogen atom to form a 3-7 membered saturated, partially unsaturated, or fully unsaturated ring having 1-2 additional heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R⁴ is Ar¹, T-Ar², or T_(n)-Ar³;

T is a C₁₋₂ alkylidene chain wherein one methylene unit of T is optionally replaced by O, NR, NRCO, NRCONR, NRCO₂, CO, CO₂, CONR, OC(O)NR, SO₂, SO₂NR, NRSO₂, NRSO₂NR, C(O)C(O), or C(O)CH₂C(O);

Ar¹ is a 5-6 membered monocyclic or 8-10 membered bicyclic saturated, partially unsaturated, or fully unsaturated ring system; wherein:

Ar¹ is optionally substituted with up to five substituents, wherein the first substituent is selected from R^x or R⁵ and wherein any additional substituents are independently selected from R⁵;

each R^x is independently selected from a 5-6 membered aryl ring having 0-3 heteroatoms selected from nitrogen, oxygen, or sulfur, wherein:

R^x is optionally substituted with 1-3 R⁵;

each R⁵ is independently selected from R, halogen, NO₂, CN, OR, SR, N(R)₂, NRC(O)R, NRC(O)N(R)₂, NRCO₂R, C(O)R, CO₂R, C(O)N(R)₂, OC(O)N(R)₂, SOR, SO₂R, SO₂N(R)₂, NRSO₂R, NRSO₂N(R)₂, C(O)C(O)R, or C(O)CH₂C(O)R;

Ar² is a 5-6 membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered saturated, partially unsaturated, or fully unsaturated bicyclic

-15-

ring system having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; wherein:

Ar² is optionally substituted with up to five substituents, wherein the first substituent is selected from R^x or R⁵ and wherein any additional substituents are independently selected from R⁵;

5 Ar³ is a 6-membered aryl ring having 0-2 nitrogens, wherein:

10 Ar³ is substituted with one Z-R⁶ group and optionally substituted with 1-3 R⁵;

Z is a C₁-C₆ alkylidene chain wherein up to two non-adjacent methylene units of Z are optionally replaced by CO, CO₂, COCO, CONR, OCONR, NRNR, NRNRCO, NRCO, NRCO₂, NRCONR, SO, SO₂, NRSO₂, SO₂NR, NRSO₂NR, O, S, or

15 NR; and

R⁶ is selected from Ar², R, halogen, NO₂, CN, OR, SR, N(R)₂, NRC(O)R, NRC(O)N(R)₂, NRCO₂R, C(O)R, CO₂R, OC(O)R, C(O)N(R)₂, OC(O)N(R)₂, SOR, SO₂R, SO₂N(R)₂, NRSO₂R, NRSO₂N(R)₂, C(O)C(O)R, or C(O)CH₂C(O)R;

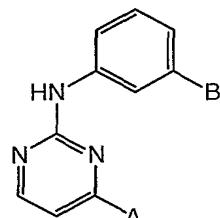
20 provided that:

(i) when R⁴ is phenyl substituted with two OR, wherein R is not hydrogen, the two OR occupy positions on the phenyl ring other than simultaneously meta and para;

and

25 (ii) said compound is other than a compound of formula

III



III

wherein:

-16-

A is a phenyl ring substituted with one or more groups selected from halogen, CN, OC(O)NH₂, CO₂R¹⁰, COR¹⁰, SO₂N(R¹⁰)₂, N(R¹⁰)₂, OR¹⁰, or fluoro-alkyl, wherein each R¹⁰ is independently selected from hydrogen or a C₁-C₇ alkyl group optionally substituted with NH₂, NH(C₁-C₇ alkyl), or N(C₁-C₇ alkyl)₂; and

B is selected from halogen, CN, OC(O)NH₂, CO₂R¹⁰, COR¹⁰, SO₂N(R¹⁰)₂, N(R¹⁰)₂, OR¹⁰, or fluoro-(C₁-C₇ alkyl).

As used herein, the following definitions shall apply unless otherwise indicated.

The phrase "optionally substituted" is used interchangeably with the phrase "substituted or unsubstituted". Unless otherwise indicated, an optionally substituted group may have a substituent at each substitutable position of the group, and each substitution is independent of the other.

The term "aliphatic" or "aliphatic group" as used herein means a straight-chain or branched C₁-C₁₂ hydrocarbon chain that is completely saturated or that contains one or more units of unsaturation, or a monocyclic C₃-C₈ hydrocarbon or bicyclic C₈-C₁₂ hydrocarbon that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic (also referred to herein as "carbocycle" or "cycloalkyl"), that has a single point of attachment to the rest of the molecule wherein any individual ring in said bicyclic ring system has 3-7 members. For example, suitable aliphatic groups include, but are not limited to, linear or branched or alkyl, alkenyl, alkynyl groups and hybrids thereof such as (cycloalkyl)alkyl, (cycloalkenyl)alkyl or (cycloalkyl)alkenyl.

The terms "alkyl", "alkoxy", "hydroxyalkyl", "alkoxyalkyl", and "alkoxycarbonyl", used alone or as part of

-17-

a larger moiety includes both straight and branched chains containing one to twelve carbon atoms. The terms "alkenyl" and "alkynyl" used alone or as part of a larger moiety shall include both straight and branched chains containing two to 5 twelve carbon atoms.

The terms "haloalkyl", "haloalkenyl" and "haloalkoxy" means alkyl, alkenyl or alkoxy, as the case may be, substituted with one or more halogen atoms. The term "halogen" means F, Cl, Br, or I.

10 The term "heteroatom" means nitrogen, oxygen, or sulfur and includes any oxidized form of nitrogen and sulfur, and the quaternized form of any basic nitrogen. Also the term "nitrogen" includes a substitutable nitrogen of a heterocyclic ring. As an example, in a saturated or partially unsaturated 15 ring having 0-3 heteroatoms selected from oxygen, sulfur or nitrogen, the nitrogen may be N (as in 3,4-dihydro-2H-pyrrolyl), NH (as in pyrrolidinyl) or NR⁺ (as in N-substituted pyrrolidinyl).

20 The term "aryl" used alone or as part of a larger moiety as in "aralkyl", "aralkoxy", or "aryloxyalkyl", refers to monocyclic, bicyclic and tricyclic ring systems having a total of five to fourteen ring members, wherein at least one ring in the system is aromatic and wherein each ring in the system contains 3 25 to 7 ring members. The term "aryl" may be used interchangeably with the term "aryl ring". The term "aryl" also refers to heteroaryl ring systems as defined hereinbelow.

30 The term "heterocycle", "heterocyclyl", or "heterocyclic" as used herein means non-aromatic, monocyclic, bicyclic or tricyclic ring systems having five to fourteen ring members in which one or more ring

-18-

members is a heteroatom, wherein each ring in the system contains 3 to 7 ring members.

The term "heteroaryl", used alone or as part of a larger moiety as in "heteroaralkyl" or

5 "heteroarylalkoxy", refers to monocyclic, bicyclic and tricyclic ring systems having a total of five to fourteen ring members, wherein at least one ring in the system is aromatic, at least one ring in the system contains one or more heteroatoms, and wherein each ring in the system
10 contains 3 to 7 ring members. The term "heteroaryl" may be used interchangeably with the term "heteroaryl ring" or the term "heteroaromatic".

An aliphatic group or a non-aromatic heterocyclic ring may contain one or more substituents. Suitable

15 substituents on the saturated carbon of an aliphatic group or of a non-aromatic heterocyclic ring are selected from halogen, oxo, -R°, -OR°, -SR°, 1,2-methylene-dioxy, 1,2-ethylenedioxy, phenyl (Ph) optionally substituted with R°, -O(Ph) optionally substituted with R°, -CH₂(Ph) optionally substituted with R°,
20 -CH₂CH₂(Ph), optionally substituted with R°, -NO₂, -CN, -N(R°)₂, -NR°C(O)R°, -NR°C(O)N(R°)₂, -NR°CO₂R°, -NR°NR°C(O)R°,
-NR°NR°C(O)N(R°)₂, -NR°NR°CO₂R°, -C(O)C(O)R°, -C(O)CH₂C(O)R°,
-CO₂R°, -C(O)R°, -C(O)N(R°)₂, -OC(O)N(R°)₂, -S(O)₂R°, -SO₂N(R°)₂,
-S(O)R°, -NR°SO₂N(R°)₂, -NR°SO₂R°, -C(=S)N(R°)₂, -C(=NH)-N(R°)₂,
25 =S, =NNHR°, =NN(R°)₂, =NNHC(O)R°, =NNHCO₂(alkyl),
=NNHSO₂(alkyl), =NR° or -(CH₂)_yNHC(O)R°, wherein each R° is independently selected from hydrogen, optionally substituted C₁₋₆ aliphatic, an unsubstituted 5-6 membered heteroaryl or heterocyclic ring, phenyl, -O(Ph), or -CH₂(Ph). Optional
30 substituents on the aliphatic group of R° are selected from NH₂, NH(C₁₋₄ aliphatic), N(C₁₋₄ aliphatic)₂, halogen, C₁₋₄

-19-

aliphatic, OH, O(C₁₋₄ aliphatic), NO₂, CN, CO₂H, CO₂(C₁₋₄ aliphatic), O(halo C₁₋₄ aliphatic), or halo C₁₋₄ aliphatic.

The term "alkylidene chain" refers to a straight or branched carbon chain that may be fully saturated or have one
5 or more units of unsaturation.

A combination of substituents or variables is permissible only if such a combination results in a stable or chemically feasible compound. A stable compound or chemically feasible compound is one that is not substantially altered
10 when kept at a temperature of 40 °C or less, in the absence of moisture or other chemically reactive conditions, for at least a week.

It will be apparent to one skilled in the art that certain compounds of this invention may exist in tautomeric
15 forms, all such tautomeric forms of the compounds being within the scope of the invention.

Unless otherwise stated, structures depicted herein are also meant to include all stereochemical forms of the structure; i.e., the R and S configurations for each
20 asymmetric center. Therefore, single stereochemical isomers as well as enantiomeric and diastereomeric mixtures of the present compounds are within the scope of the invention.

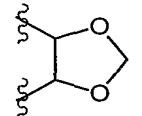
Unless otherwise stated, structures depicted herein are also meant to include compounds which differ only in the presence
25 of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement of a hydrogen by a deuterium or tritium, or the replacement of a carbon by a ¹³C- or ¹⁴C-enriched carbon are within the scope of this invention.

30 Preferred R¹, R², and R³ groups of formulae I and II are selected from halogen, QR or QAr², wherein Q is a C₁₋₃ alkylidene chain wherein one methylene unit of Q is optionally replaced by -O-, -S-, -NHCO-, or -NR-, and Ar²

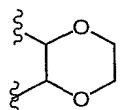
-20-

is an optionally substituted 5-6 membered saturated, partially unsaturated, or fully unsaturated ring having 0-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Most preferred R¹, R², and R³ groups are selected from OH, OCH₃, OCH₂CH₃, NHCOMe, NH₂, NH(C₁₋₄ aliphatic), N(C₁₋₄ aliphatic)₂, O(CH₂)₂morpholin-4-yl, O(CH₂)₂NH₂, O(CH₂)₂NH(C₁₋₄ aliphatic), O(CH₂)₂N(C₁₋₄ aliphatic)₂, bromo, chloro, or fluoro. Other preferred compounds of formulae I and II are those where either R¹

10 and R², or R² and R³ are taken together to form



or



. Most preferred Ar² groups are morpholin-4-yl, pyrrolidin-1-yl, piperidin-1-yl, thiomorpholin-4-yl, pyrazol-1-yl, or imidazol-1-yl.

Preferred R⁴ groups of formulae I and II are selected from a 6-membered saturated, partially unsaturated, or aryl ring having 0-3 nitrogens, a 9-10 membered bicyclic aryl ring having 0-2 nitrogens, or a 5 membered heteroaryl ring having 2-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein each ring is optionally substituted. More preferred R⁴ groups of formulae I and II are substituted rings selected from phenyl, cyclohexyl, naphthyl, pyridyl, pyrimidinyl, triazinyl, thiazolyl, thiadiazolyl, pyrazolyl, isoxazolyl, indazolyl, or benzimidazolyl.

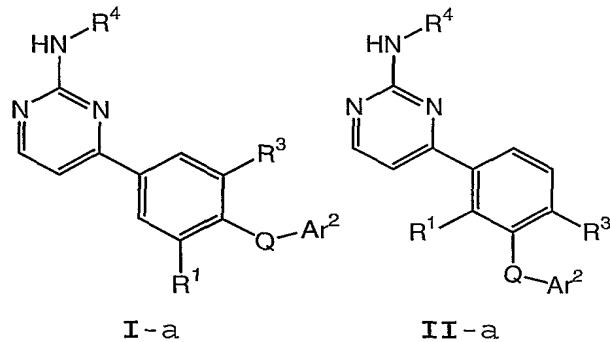
Preferred substituents on R⁴ are independently selected from R, halogen, NO₂, OR, N(R)₂, R^x, or Z-R⁶, wherein R is hydrogen or optionally substituted C₁₋₄ aliphatic.

Preferred Z groups of formulae I and II are selected from a C₁₋₄ alkylidene chain wherein one methylene unit of Z is optionally replaced by -O-, -S-, -SO₂-, or -NH-. Preferred R⁶

-21-

groups are selected from optionally substituted phenyl, pyridyl, and pyrimidinyl. Preferred R^x substituents on R⁴ are selected from phenyl, pyridyl, and pyrimidinyl wherein R^x is optionally substituted with 1-2 R⁵. More preferred 5 substituents on R⁴ are selected from chloro, fluoro, bromo, methyl, ethyl, t-butyl, isopropyl, cyclopropyl, nitro, OMe, OEt, CF₃, NH₂, benzyl, benzyloxy, OH, methylene dioxy, SO₂NH₂, phenoxy, O-pyridinyl, SO₂phenyl, nitrophenoxy, aminophenoxy, S-dimethylpyrimidine, NHphenyl, NH-methoxyphenyl, pyridinyl, 10 aminophenyl, phenol, chloro-fluoro-phenyl, dimethylaminophenyl, CF₃-phenyl, dimethylphenyl, chlorophenyl, fluorophenyl, methoxyphenoxy, chlorophenoxy, ethoxyphenoxy, and fluorophenoxy. Most preferred R⁴ groups of formulae I and II are those depicted in Tables 1, 2, and 3.

15 A preferred embodiment relates to a compound of formula I-a or II-a:

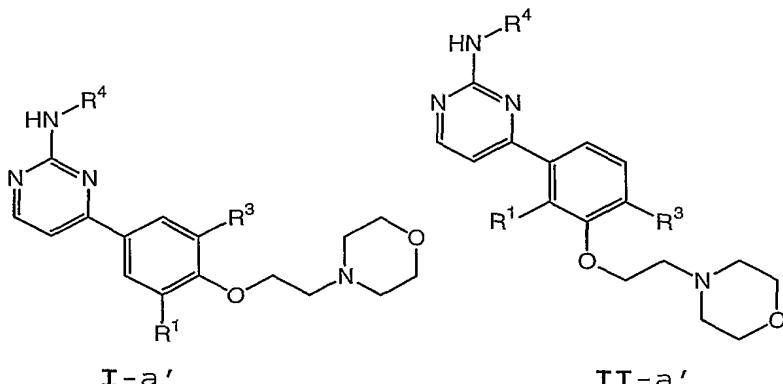


or a pharmaceutically acceptable derivative thereof, 20 wherein R¹, R³, R⁴, Q, and Ar² are as defined above.

Preferred R¹, R³, R⁴, Ar², and Q are as described above for compounds of formulae I and II.

Most preferred compounds of I-a and II-a are those of formula I-a' and II-a':

-22-

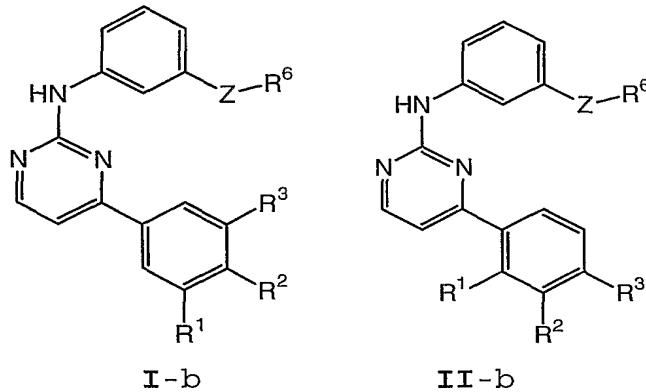


or a pharmaceutically acceptable derivative thereof,
wherein R¹, R³, and R⁴ are as defined above.

5 Preferred R¹, R³, and R⁴ groups of formulae I-a'
and II-a' are those described above for compounds of
formulae I and II.

Another preferred embodiment relates to a
compound of formula I-b or II-b:

10



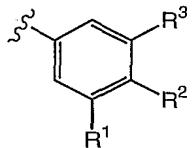
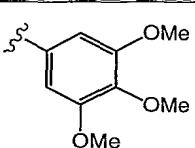
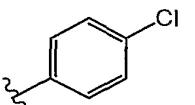
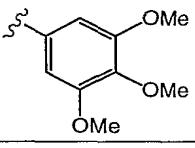
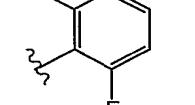
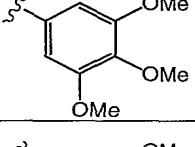
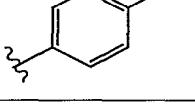
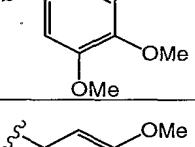
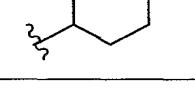
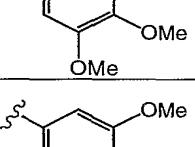
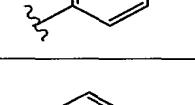
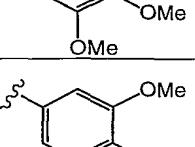
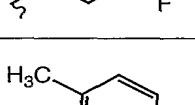
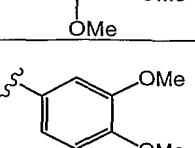
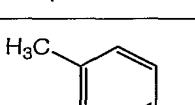
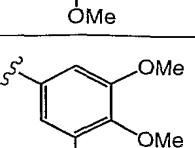
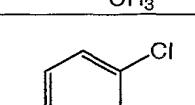
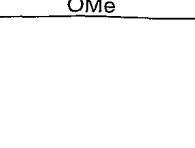
or a pharmaceutically acceptable derivative thereof,
wherein R¹, R², R³, Z, and R⁶ are as defined above.

15 Preferred R¹, R², R³, Z, and R⁶ are as described
above for compounds of formulae I and II.

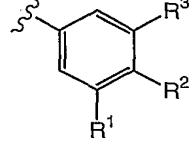
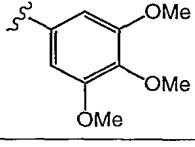
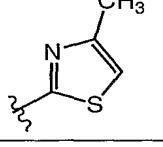
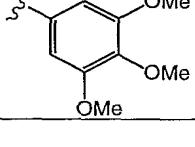
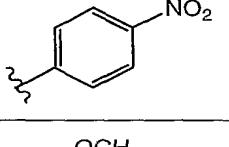
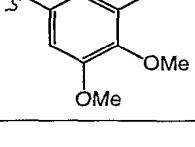
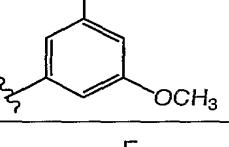
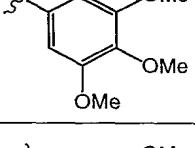
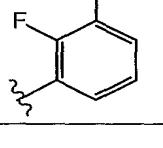
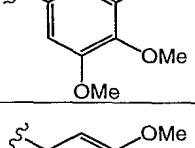
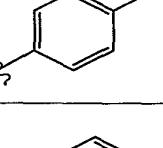
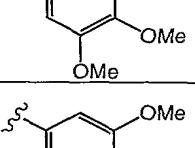
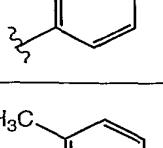
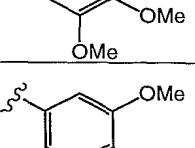
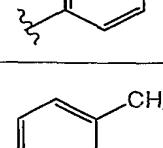
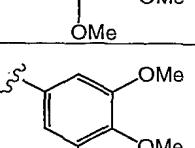
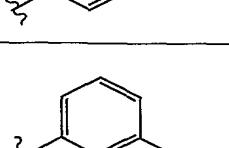
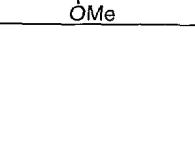
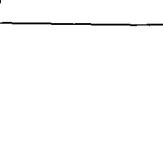
Exemplary structures of formula I, wherein W is
nitrogen, are set forth in Table 1 below.

- 23 -

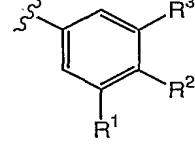
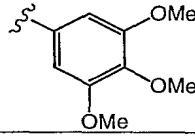
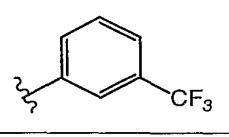
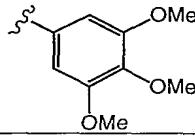
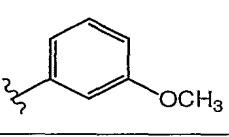
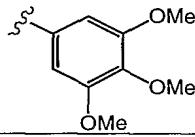
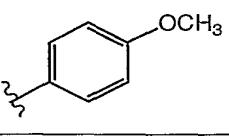
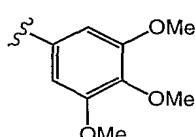
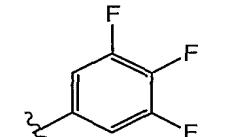
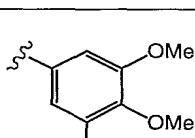
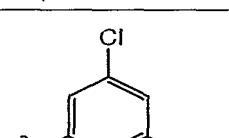
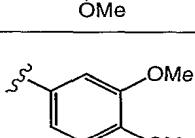
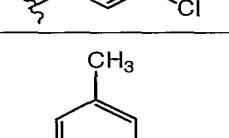
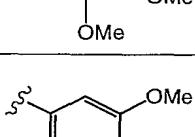
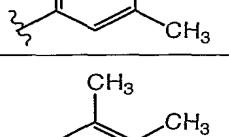
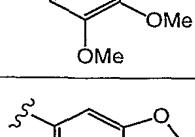
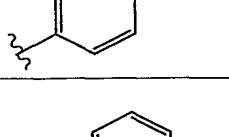
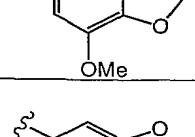
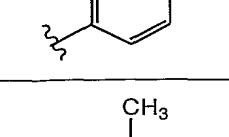
Table 1. Compounds of Formula I

No.		R ⁴
I-1		
I-2		
I-3		
I-4		
I-5		
I-6		
I-7		
I-8		
I-9		

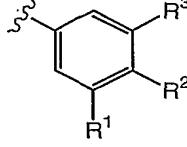
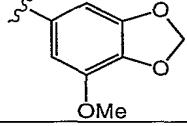
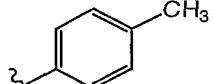
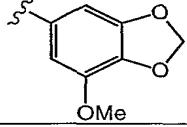
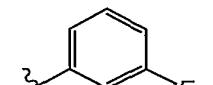
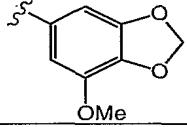
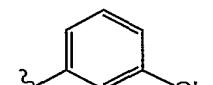
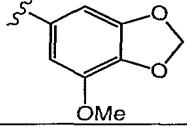
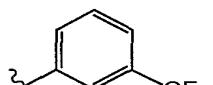
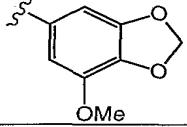
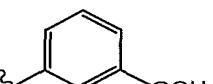
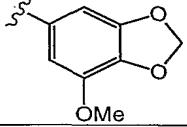
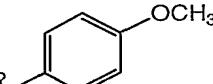
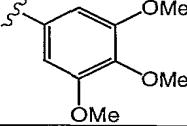
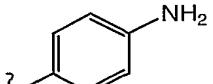
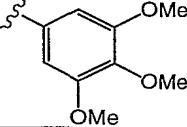
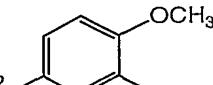
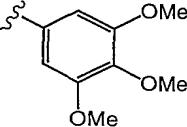
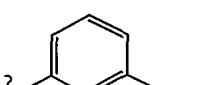
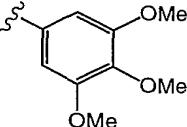
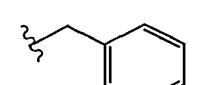
- 24 -

No.		R ⁴
I-10		
I-11		
I-12		
I-13		
I-14		
I-15		
I-16		
I-17		
I-18		

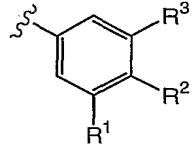
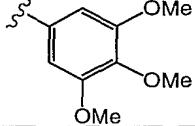
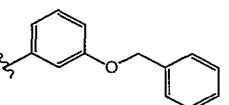
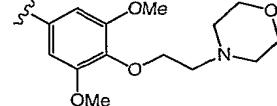
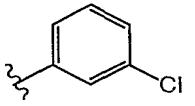
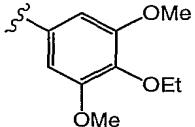
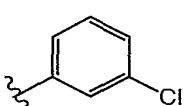
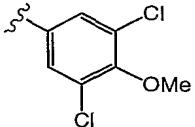
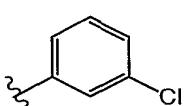
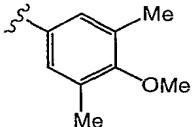
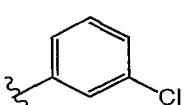
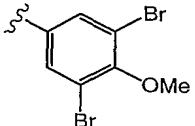
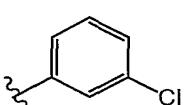
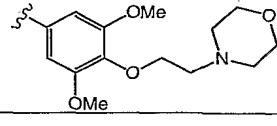
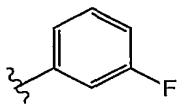
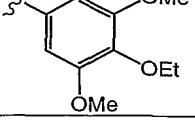
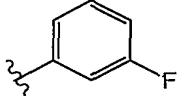
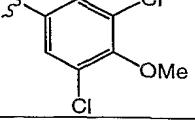
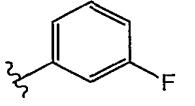
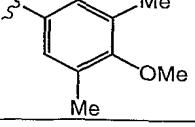
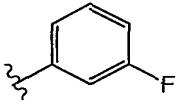
-25-

No.		R ⁴
I-19		
I-20		
I-21		
I-22		
I-23		
I-24		
I-25		
I-26		
I-27		

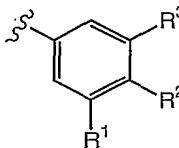
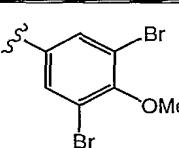
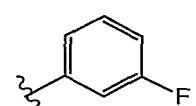
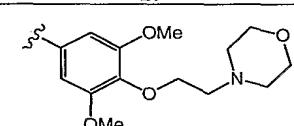
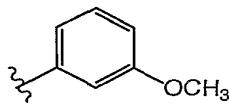
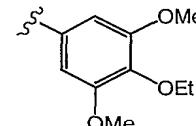
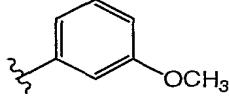
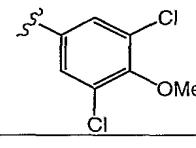
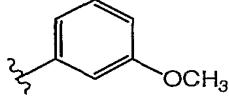
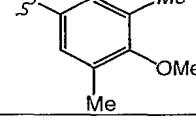
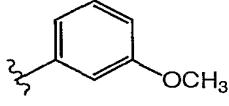
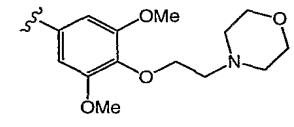
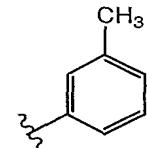
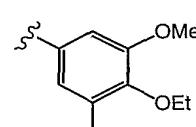
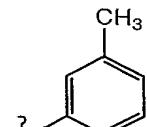
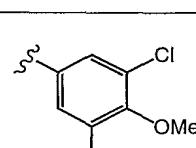
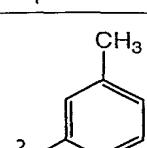
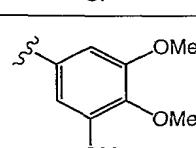
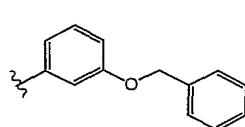
- 26 -

No.		R ⁴
I-28		
I-29		
I-30		
I-31		
I-32		
I-33		
I-34		
I-35		
I-36		
I-37		

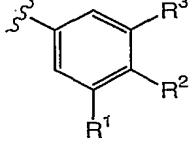
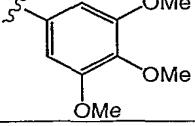
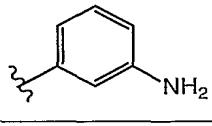
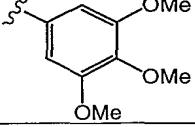
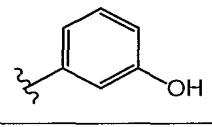
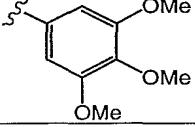
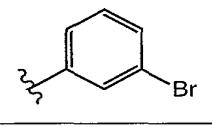
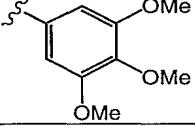
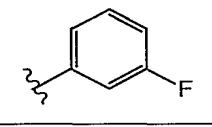
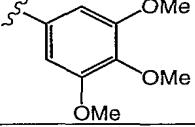
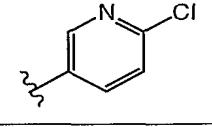
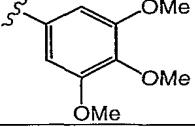
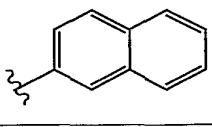
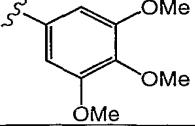
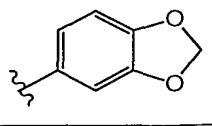
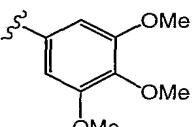
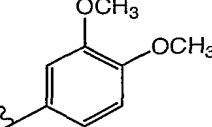
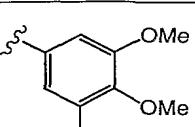
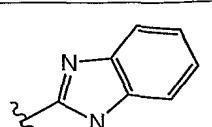
- 27 -

No.		R ⁴
I-38		
I-39		
I-40		
I-41		
I-42		
I-43		
I-44		
I-45		
I-46		
I-47		

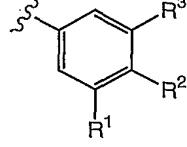
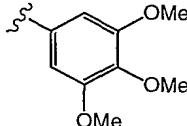
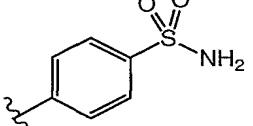
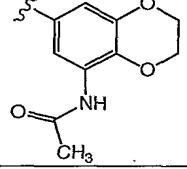
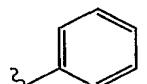
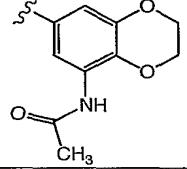
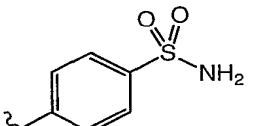
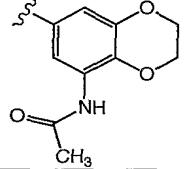
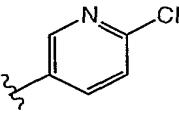
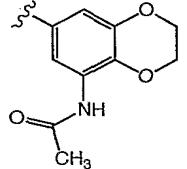
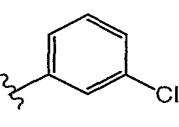
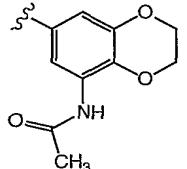
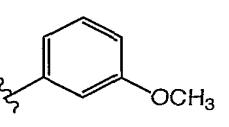
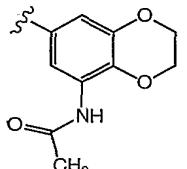
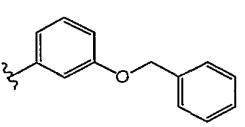
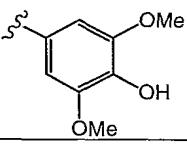
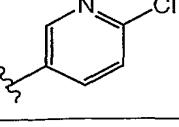
-28-

No.		R ⁴
I-48		
I-49		
I-50		
I-51		
I-52		
I-53		
I-54		
I-55		
I-56		

- 29 -

No.		R ⁴
I-57		
I-58		
I-59		
I-60		
I-61		
I-62		
I-63		
I-64		
I-65		

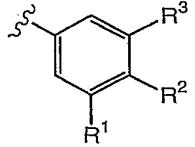
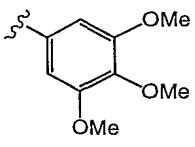
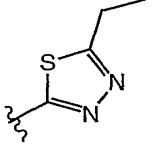
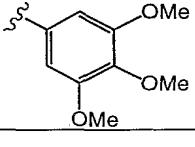
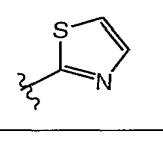
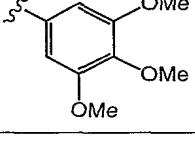
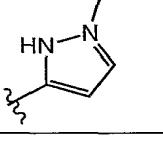
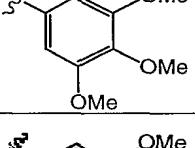
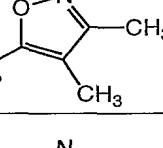
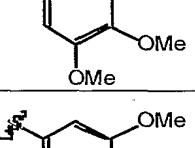
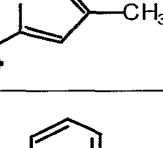
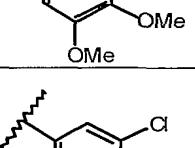
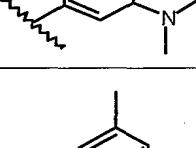
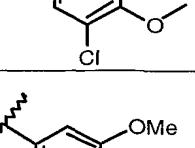
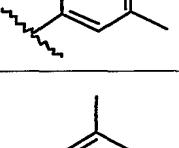
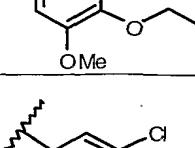
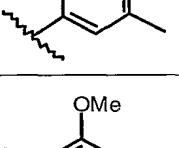
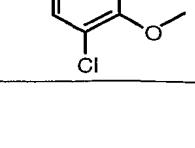
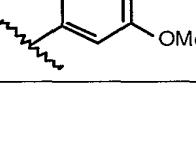
- 30 -

No.		R ⁴
I-66		
I-67		
I-68		
I-69		
I-70		
I-71		
I-72		
I-73		

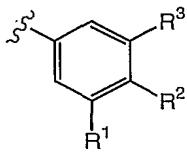
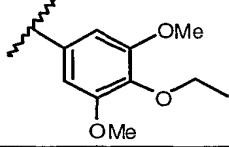
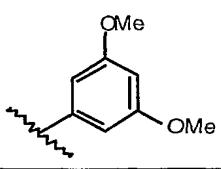
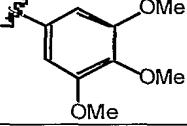
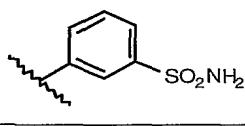
- 31 -

No.		R ⁴
I-74		
I-75		
I-76		
I-77		
I-78		
I-79		
I-80		
I-81		
I-82		
I-83		

- 32 -

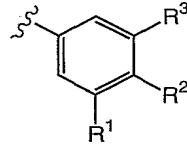
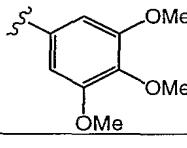
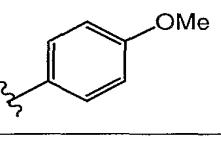
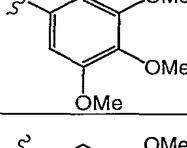
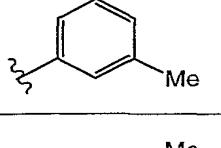
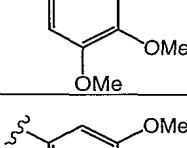
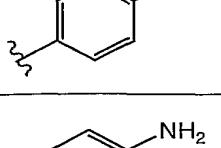
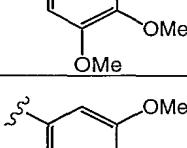
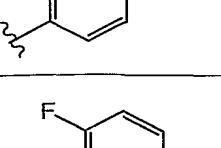
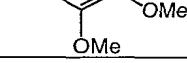
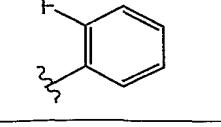
No.		R ⁴
I-84		
I-85		
I-86		
I-87		
I-88		
I-89		
I-90		
I-91		
I-92		

-33-

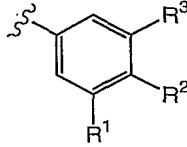
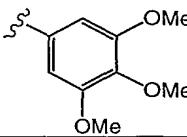
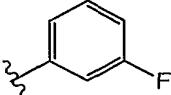
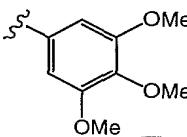
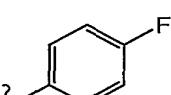
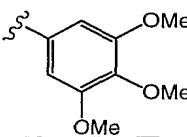
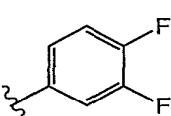
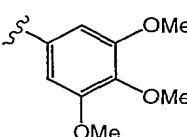
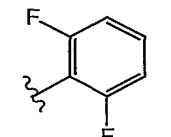
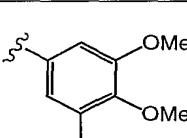
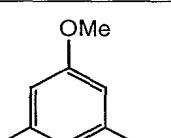
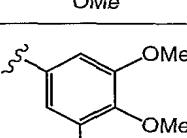
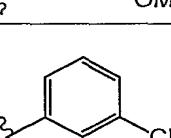
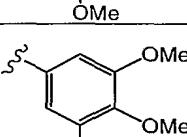
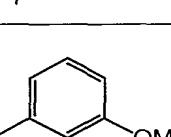
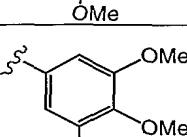
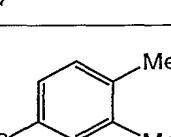
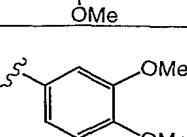
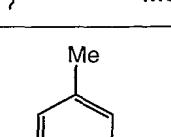
No.		R ⁴
I-93		
I-94		

Exemplary structures of formula I, wherein W is CH, are set forth in Table 2 below.

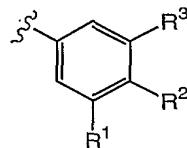
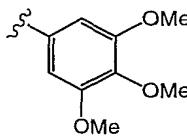
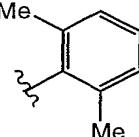
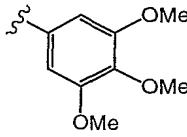
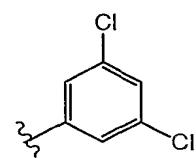
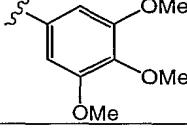
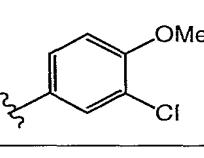
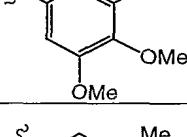
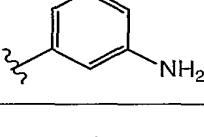
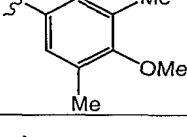
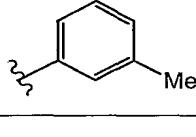
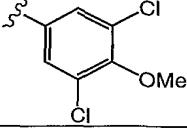
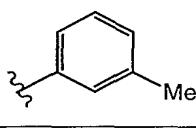
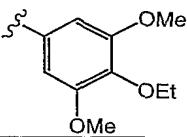
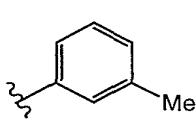
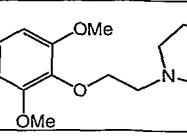
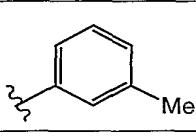
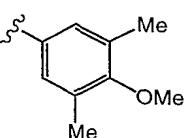
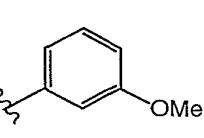
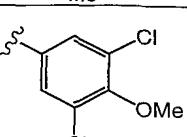
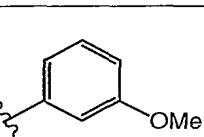
5 Table 2. Compounds of Formula I

No.		R ⁴
I-96		
I-97		
I-98		
I-99		
I-100		

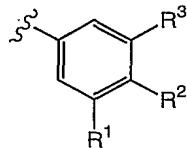
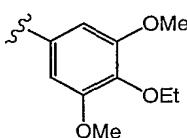
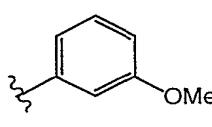
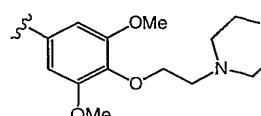
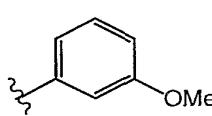
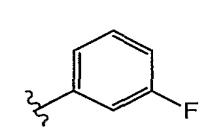
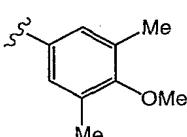
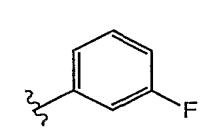
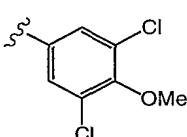
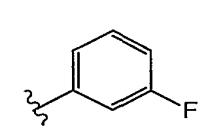
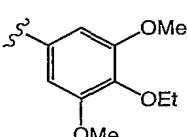
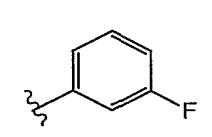
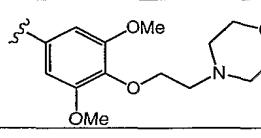
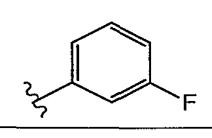
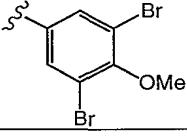
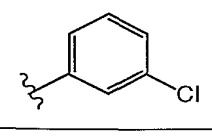
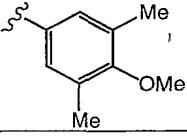
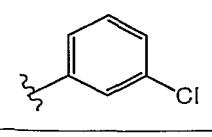
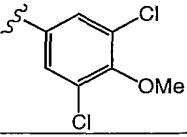
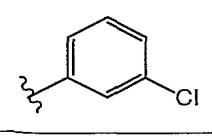
- 34 -

No.		R ⁴
I-101		
I-102		
I-103		
I-104		
I-105		
I-106		
I-107		
I-108		
I-109		

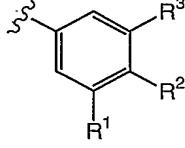
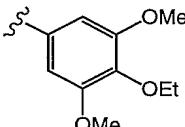
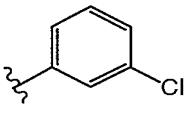
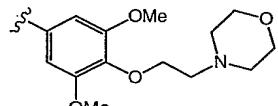
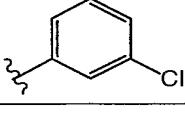
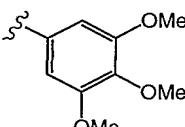
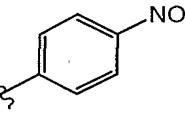
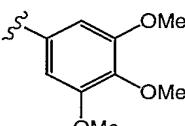
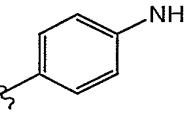
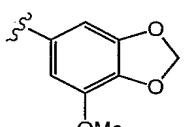
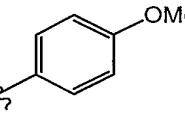
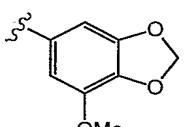
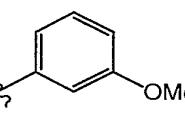
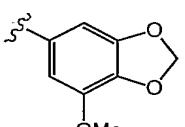
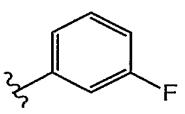
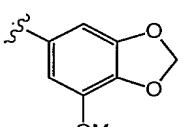
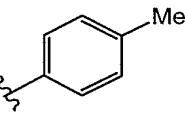
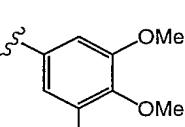
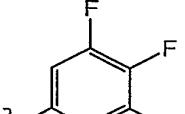
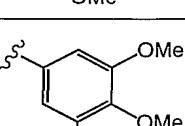
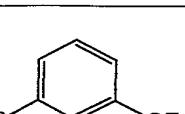
- 35 -

No.		R ⁴
I-110		
I-111		
I-112		
I-113		
I-114		
I-115		
I-116		
I-117		
I-118		
I-119		

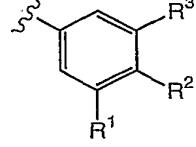
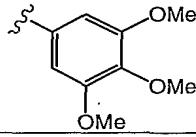
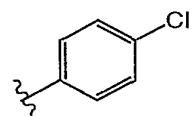
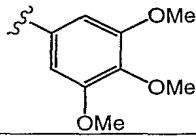
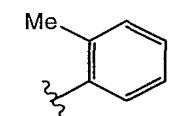
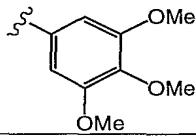
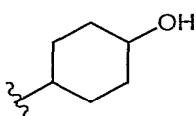
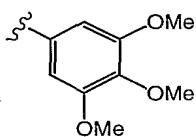
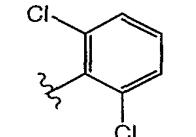
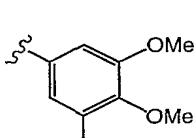
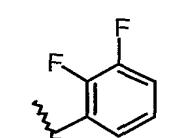
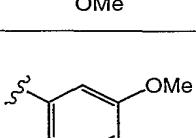
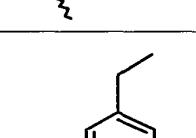
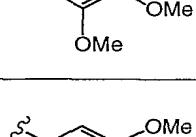
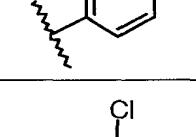
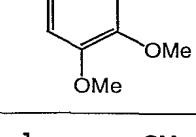
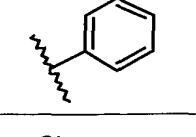
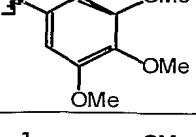
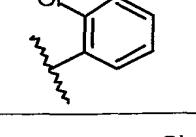
- 36 -

No.		R ⁴
I-120		
I-121		
I-122		
I-123		
I-124		
I-125		
I-126		
I-127		
I-128		
I-129		

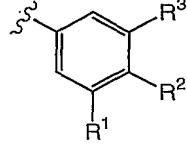
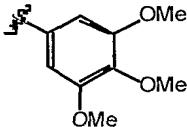
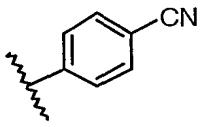
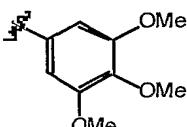
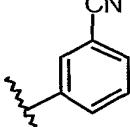
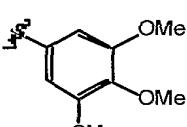
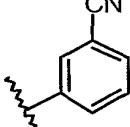
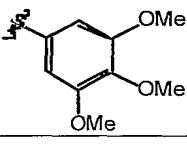
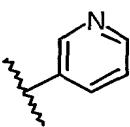
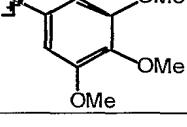
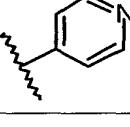
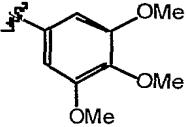
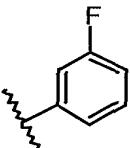
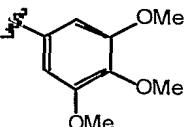
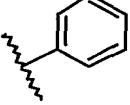
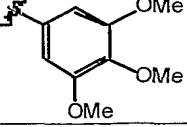
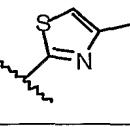
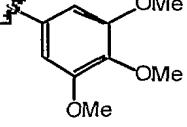
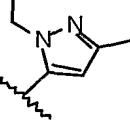
- 37 -

No.		R⁴
I-130		
I-131		
I-132		
I-133		
I-134		
I-135		
I-136		
I-137		
I-138		
I-139		

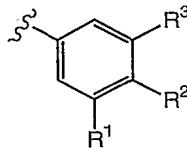
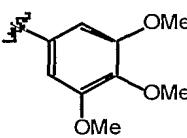
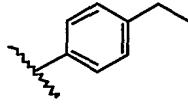
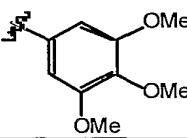
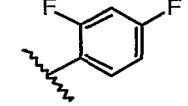
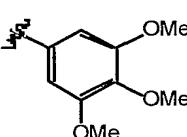
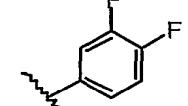
- 38 -

No.		R ⁴
I-140		
I-141		
I-142		
I-143		
I-144		
I-145		
I-146		
I-147		
I-148		

- 39 -

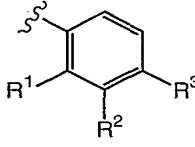
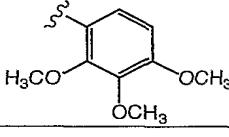
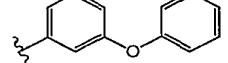
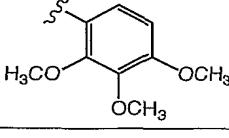
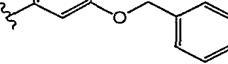
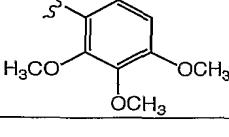
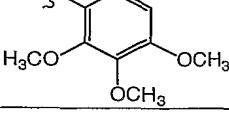
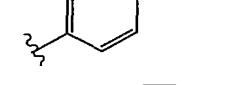
No.		R ⁴
I-149		
I-150		
I-151		
I-152		
I-153		
I-154		
I-155		
I-156		
I-157		

- 40 -

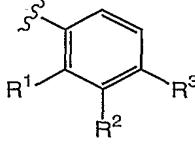
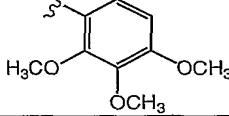
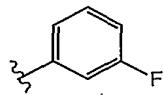
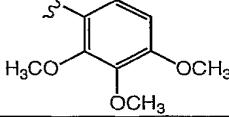
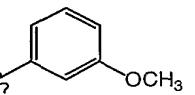
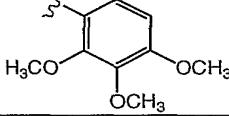
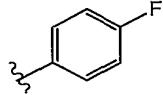
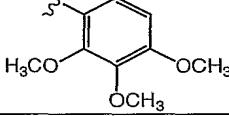
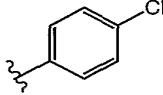
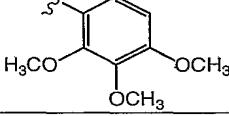
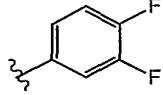
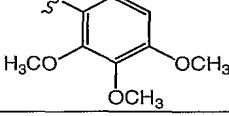
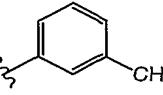
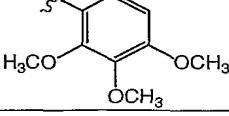
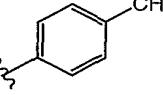
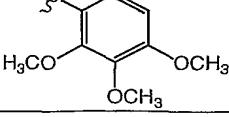
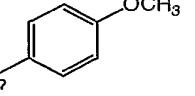
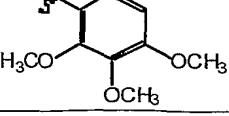
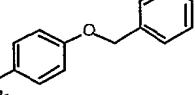
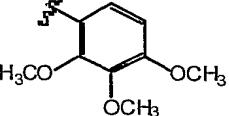
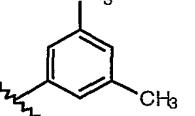
No.		R ⁴
I-158		
I-159		
I-160		

Exemplary structures of formula II, wherein W is nitrogen, are set forth in Table 3 below.

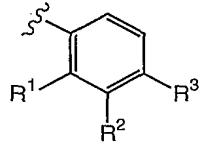
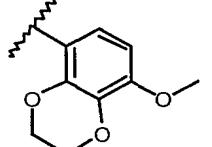
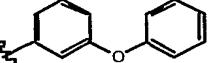
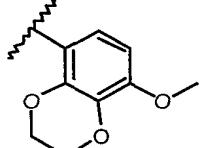
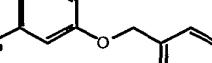
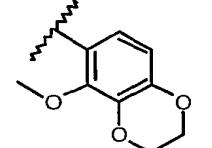
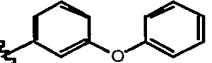
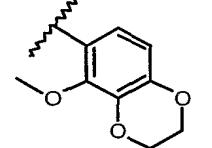
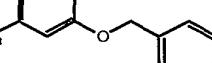
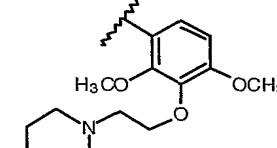
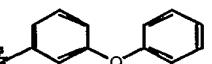
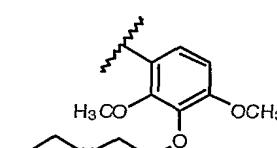
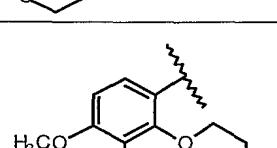
5 Table 3. Compounds of Formula II

No.		TR ⁴
II-1		
II-2		
II-3		
II-4		

-41-

No.		TR ⁴
II-5		
II-6		
II-7		
II-8		
II-9		
II-10		
II-11		
II-12		
II-13		
II-14		

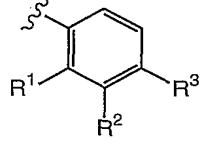
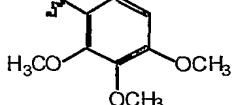
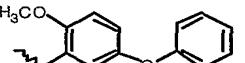
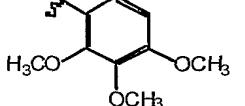
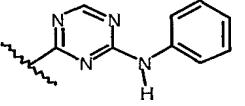
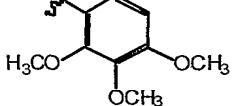
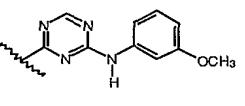
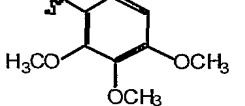
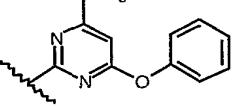
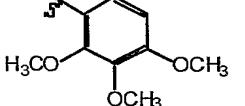
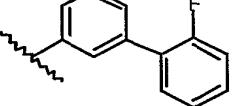
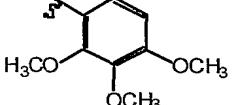
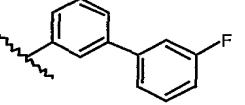
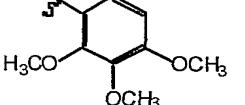
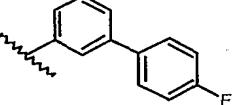
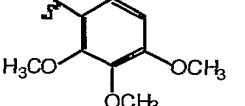
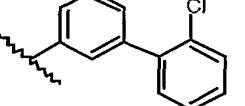
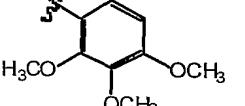
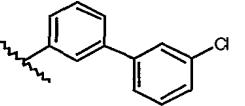
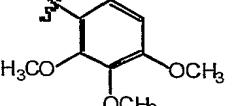
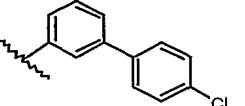
- 42 -

No.		TR ⁴
II-15		
II-16		
II-17		
II-18		
II-19		
II-20		
II-21		

-43-

No.		TR ⁴
II-22		
II-23		
II-24		
II-25		
II-26		
II-27		
II-28		
II-29		
II-30		

- 44 -

No.		TR ⁴
II-31		
II-32		
II-33		
II-34		
II-35		
II-36		
II-37		
II-38		
II-39		
II-40		

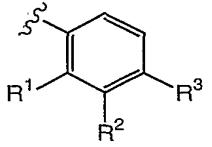
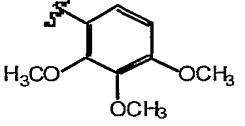
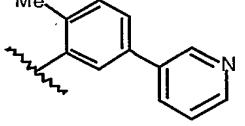
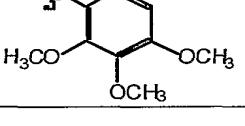
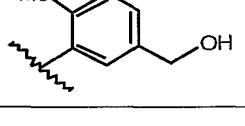
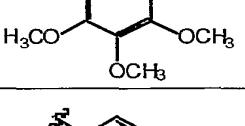
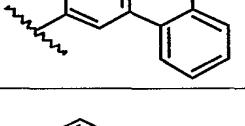
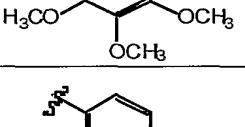
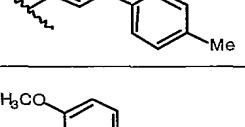
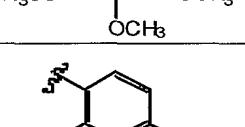
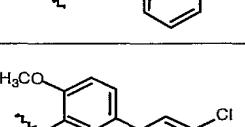
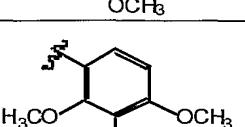
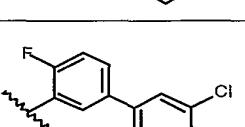
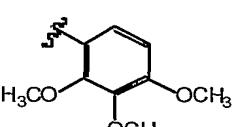
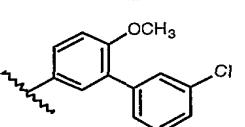
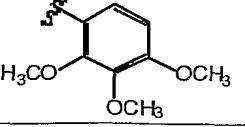
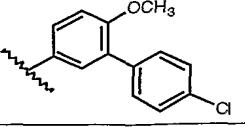
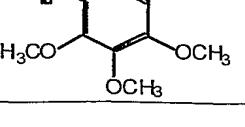
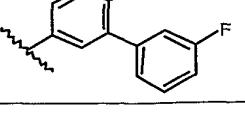
-45-

No.		TR ⁴
II-41		
II-42		
II-43		
II-44		
II-45		
II-46		
II-47		
II-48		
II-49		
II-50		

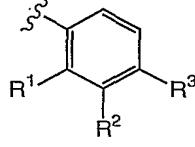
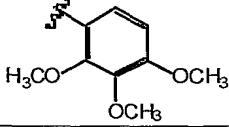
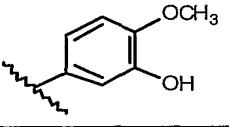
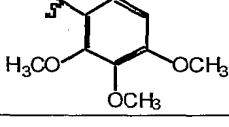
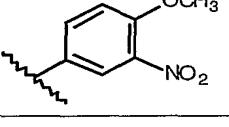
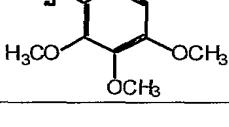
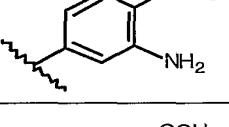
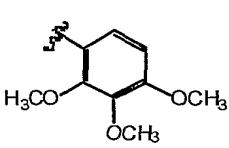
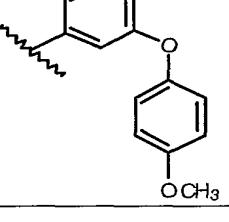
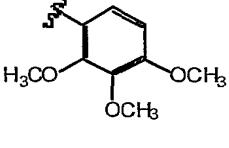
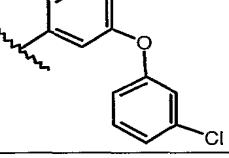
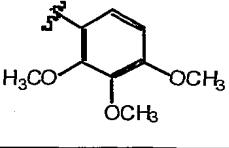
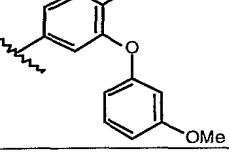
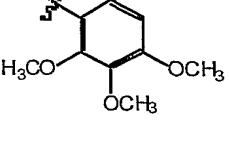
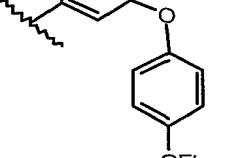
- 46 -

No.		TR ⁴
II-51		
II-52		
II-53		
II-54		
II-55		
II-56		
II-57		
II-58		
II-59		

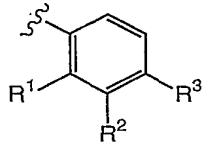
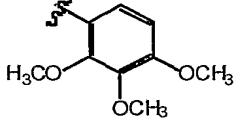
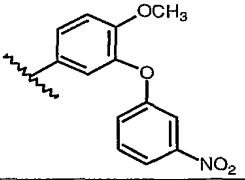
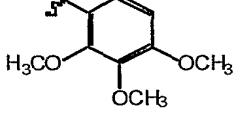
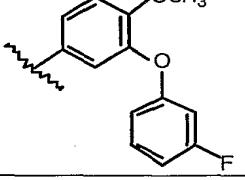
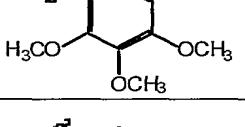
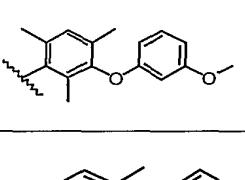
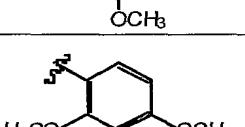
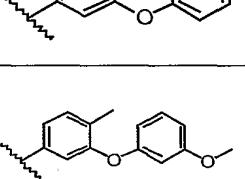
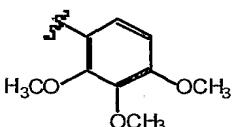
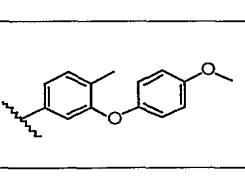
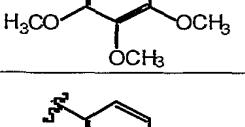
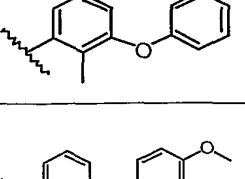
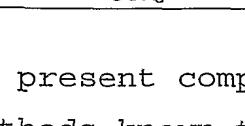
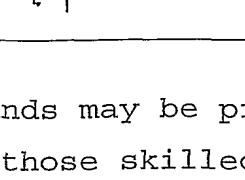
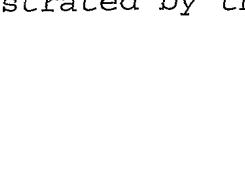
- 47 -

No.		TR ⁴
II-60		
II-61		
II-62		
II-63		
II-64		
II-65		
II-66		
II-67		
II-68		
II-69		

- 48 -

No.		TR ⁴
II-70		
II-71		
II-72		
II-73		
II-74		
II-75		
II-76		

- 49 -

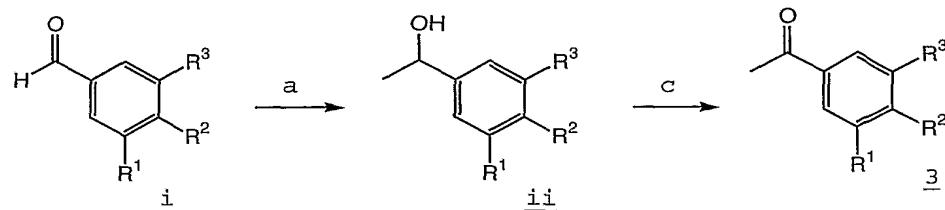
No.		TR ⁴
II-77		
II-78		
II-79		
II-80		
II-81		
II-82		
II-83		
II-84		

The present compounds may be prepared in general by methods known to those skilled in the art for analogous compounds, as illustrated by the general

-50-

Schemes I through IV, and the synthetic examples shown below.

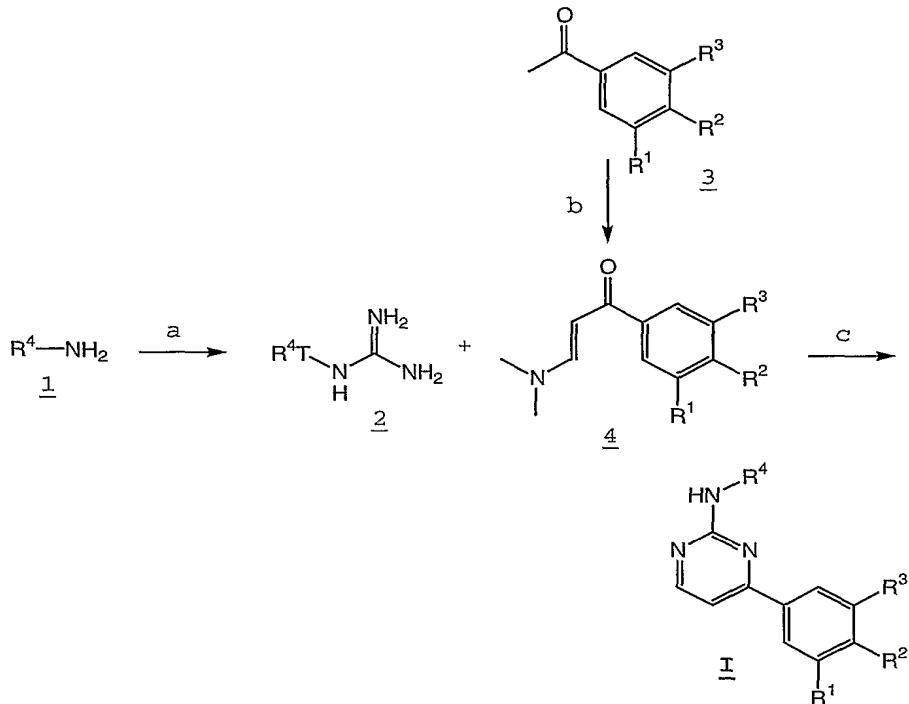
Scheme I



5 Reagents and conditions: (a) MeMgCl, THF, -78 °C; (b)
 MnO₂, CH₂Cl₂, reflux;

10 Scheme I above shows a general synthetic route used for preparing the intermediate compound 3. To a solution of aldehyde (i) in THF, at -78 °C, is added a solution of methyl magnesium chloride in THF. The reaction is quenched with cold HCl (1N), then aqueous work-up followed by chromatography affords alcohol (ii).
 15 Manganese dioxide is added to a solution of ii in CH₂Cl₂ and the resulting mixture is heated to reflux. After 3 hours, the suspension is filtered through Celite® and the filtrate concentrated *in vacuo* to afford ketone (3).

-51-

Scheme II

Reagents and conditions: (a) NH_2NCN , HCl , 1,4-dioxane;
 (b) DMF-DMA, 80°C , 12-18 hours; (c) acetonitrile,
 reflux.

5

Scheme II above shows a general synthetic route used for preparing compounds of formula I. Aniline 1 is combined with cyanamide, HCl (4N in 1,4-dioxane), and 1,4-dioxane in sealed tube and the resulting mixture heated at 60°C . After 12-18 hours, aqueous work-up affords the desired guanidine derivative (2).

Intermediate 4 is prepared from dissolving 3 in N,N -dimethylformamide dimethylacetal (DMF-DMA) and heating the resulting solution at 80°C . The reaction is concentrated *in vacuo* and the crude product recrystallized to afford enaminone 4.

Enaminone 4 was combined with guanidine 2 and acetonitrile and the resulting mixture heated at 80°C . After aqueous work-up, the crude product is purified by

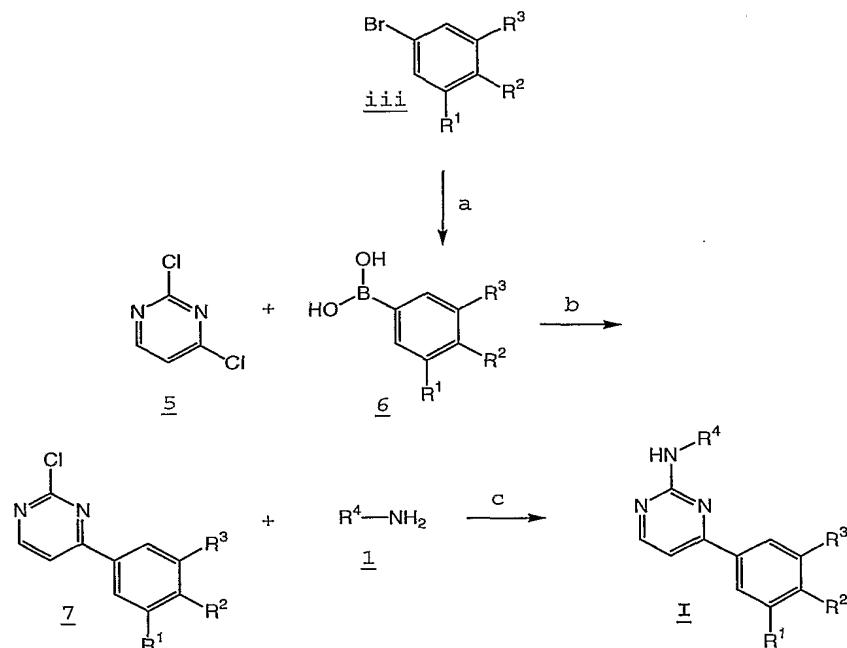
20

-52-

chromatography to afford **I** in 50-95% yield, depending upon the guanidine derivative used.

A variety of R¹, R², R³, and R⁴ are amenable to the reaction conditions described above for Scheme II, 5 including those listed above in Table 1.

Scheme III



Reagents and conditions: (a) Mg, I₂, THF, trimethylborate; room temperature, 12-18 hours; (b) Na₂CO₃, Pd(PPh₃)₄, toluene:methanol (4:1), reflux, 24 hours; (c) NaH (60% dispersion in mineral oil), Pd(PPh₃)₄, THF, reflux, 3 hours.

15 Scheme III above shows an alternate method for preparing compounds of formula **I**. The aryl boronic acid **(6)** is prepared from treating the bromide **iii** with magnesium turnings, and a catalytic amount of iodine, in THF at reflux for 12-18 hours. The reaction is cooled to 20 0°C then trimethyl borate is added and the resulting mixture stirred at room temperature for 12-18 hours. The reaction is hydrolyzed with HCl (6N, aqueous) at 60°C then aqueous work-up afforded the desired boronic acid **6**.

-53-

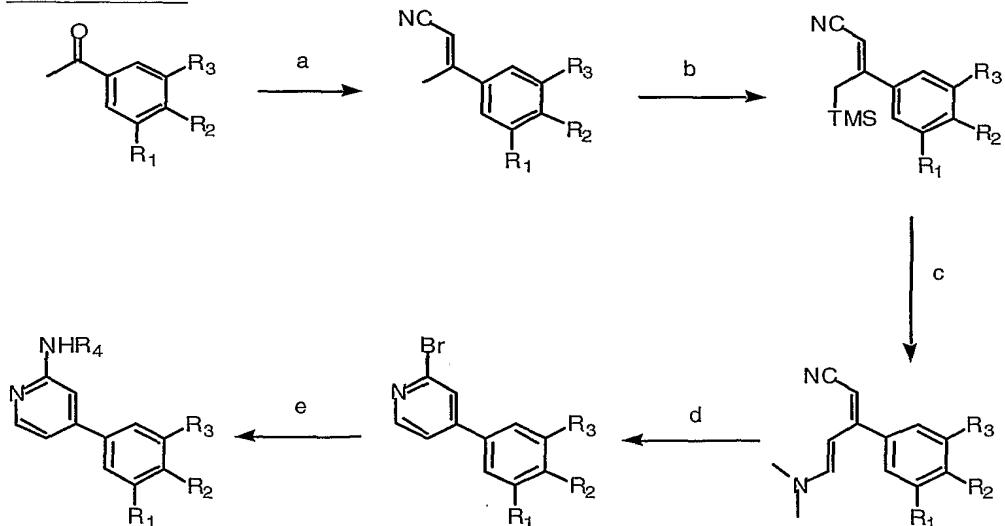
The boronic acid 6 is combined with the dichloropyrimidine (5), Na₂CO₃, and Pd(PPh₃)₄ in a solution of toluene:methanol (4:1). The resulting mixture is heated at reflux for 24 hours then filtered through 5 silica gel. The crude product is purified by flash chromatography to afford chloropyrimidine 7.

The chloropyrimidine 7 is combined with the aniline 1, NaH (60% dispersion in mineral oil), and Pd(PPh₃)₄ in THF and the resulting mixture heated at 10 reflux for 3 hours. The reaction is cooled then poured into water. Aqueous work-up, followed by flash chromatography affords **I**. A variety of R¹, R², R³, and R⁴ are amenable to the reaction conditions described above for Scheme III, including those listed above in Table 1.

Compounds of formula **I** wherein W is CH may also be synthesized by methods essentially similar to those described above at Scheme III, by methods shown in Scheme IV below, and by methods known to one of skill in the art.

20

Scheme IV



Reagents and conditions: (a) NCCH₂P(O)(OEt)₂, NaH, THF; (b) lithium hexamethyldisilazide, THF then trimethylsilyl chloride; (c) dimethylformamide dimethylacetal; (d)

25

-54-

gaseous HBr, CHCl₃; e) R⁴NH₂, NaH, dimethylformamide, 80°C.

The details of the conditions used for producing these compounds are set forth in the Examples.

- 5 One having ordinary skill in the art may synthesize other compounds of this invention following the teachings of the specification using reagents that are readily synthesized or commercially available.

The activity of a compound utilized in this invention as an inhibitor of JNK3, GSK-3, CDK2, Lck, or Src, may be assayed *in vitro*, *in vivo* or in a cell line. *In vitro* assays include assays that determine inhibition of either the phosphorylation activity or ATPase activity of activated JNK3, GSK-3, CDK2, Lck, or Src. Alternate 15 *in vitro* assays quantitate the ability of the inhibitor to bind to JNK3, GSK-3, CDK2, Lck, or Src. Inhibitor binding may be measured by radiolabelling the inhibitor prior to binding, isolating the inhibitor/JNK3, inhibitor/GSK-3, inhibitor/CDK2, inhibitor/Lck, or 20 inhibitor/Src complex and determining the amount of radiolabel bound. Alternatively, inhibitor binding may be determined by running a competition experiment where new inhibitors are incubated with JNK3, GSK-3, CDK2, Lck, or Src bound to known radioligands.

25 According to another embodiment, the invention provides a composition comprising a compound of this invention or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier, adjuvant, or vehicle. The amount of compound in the compositions of 30 this invention is such that is effective to detectably inhibit a protein kinase, particularly JNK3, GSK-3, CDK2, Lck, or Src in a biological sample or in a patient. Preferably the composition of this invention is formulated for administration to a patient in need of

-55-

such composition. Most preferably, the composition of this invention is formulated for oral administration to a patient.

The term "patient", as used herein, means an
5 animal, preferably a mammal, and most preferably a human.

The term "pharmaceutically acceptable carrier, adjuvant, or vehicle" refers to a non-toxic carrier, adjuvant, or vehicle that does not destroy the pharmacological activity of the compound with which it is
10 formulated. Pharmaceutically acceptable carriers, adjuvants or vehicles that may be used in the compositions of this invention include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin,
15 buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium
20 chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers,
25 polyethylene glycol and wool fat.

The term "detectably inhibit", as used herein means a measurable change in JNK3, GSK-3, CDK2, Lck, or Src activity between a sample comprising said composition and a JNK3, GSK-3, CDK2, Lck, or Src kinase and an
30 equivalent sample comprising JNK3, GSK-3, CDK2, Lck, or Src kinase in the absence of said composition.

A "pharmaceutically acceptable salt" means any non-toxic salt, ester, salt of an ester or other

-56-

derivative of a compound of this invention that, upon administration to a recipient, is capable of providing, either directly or indirectly, a compound of this invention or an inhibitorily active metabolite or residue 5 thereof.

Pharmaceutically acceptable salts of the compounds of this invention include those derived from pharmaceutically acceptable inorganic and organic acids and bases. Examples of suitable acid salts include 10 acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptanoate, glycerophosphate, glycolate, 15 hemisulfate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oxalate, palmoate, pectinate, persulfate, 3-phenylpropionate, 20 phosphate, picrate, pivalate, propionate, salicylate, succinate, sulfate, tartrate, thiocyanate, tosylate and undecanoate. Other acids, such as oxalic, while not in themselves pharmaceutically acceptable, may be employed in the preparation of salts useful as intermediates in 25 obtaining the compounds of the invention and their pharmaceutically acceptable acid addition salts.

Salts derived from appropriate bases include alkali metal (e.g., sodium and potassium), alkaline earth metal (e.g., magnesium), ammonium and $N^+(C_{1-4} \text{ alkyl})_4$ 30 salts. This invention also envisions the quaternization of any basic nitrogen-containing groups of the compounds disclosed herein. Water or oil-soluble or dispersible products may be obtained by such quaternization.

-57-

The compositions of the present invention may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir. The term "parenteral" as used herein includes subcutaneous, intravenous, intramuscular, intra-articular, intra-synovial, intrasternal, intrathecal, intrahepatic, intralesional and intracranial injection or infusion techniques.

Preferably, the compositions are administered orally, intraperitoneally or intravenously. Sterile injectable forms of the compositions of this invention may be aqueous or oleaginous suspension. These suspensions may be formulated according to techniques known in the art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium.

For this purpose, any bland fixed oil may be employed including synthetic mono- or di-glycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant, such as carboxymethyl cellulose or similar dispersing agents that are commonly used in the

-58-

formulation of pharmaceutically acceptable dosage forms including emulsions and suspensions. Other commonly used surfactants, such as Tweens, Spans and other emulsifying agents or bioavailability enhancers which are commonly 5 used in the manufacture of pharmaceutically acceptable solid, liquid, or other dosage forms may also be used for the purposes of formulation.

The pharmaceutically acceptable compositions of this invention may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, aqueous suspensions or solutions. In the case of tablets for oral use, carriers commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. 10 For oral administration in a capsule form, useful diluents include lactose and dried cornstarch. When aqueous suspensions are required for oral use, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening, flavoring or 15 coloring agents may also be added. 20

Alternatively, the pharmaceutically acceptable compositions of this invention may be administered in the form of suppositories for rectal administration. These can be prepared by mixing the agent with a suitable non-irritating excipient that is solid at room temperature 25 but liquid at rectal temperature and therefore will melt in the rectum to release the drug. Such materials include cocoa butter, beeswax and polyethylene glycols.

The pharmaceutically acceptable compositions of this invention may also be administered topically, especially when the target of treatment includes areas or organs readily accessible by topical application, including diseases of the eye, the skin, or the lower 30

-59-

intestinal tract. Suitable topical formulations are readily prepared for each of these areas or organs.

Topical application for the lower intestinal tract can be effected in a rectal suppository formulation

5 (see above) or in a suitable enema formulation.

Topically-transdermal patches may also be used.

For topical applications, the pharmaceutically acceptable compositions may be formulated in a suitable ointment containing the active component suspended or

10 dissolved in one or more carriers. Carriers for topical administration of the compounds of this invention include, but are not limited to, mineral oil, liquid

petrolatum, white petrolatum, propylene glycol, polyoxyethylene, polyoxypropylene compound, emulsifying

15 wax and water. Alternatively, the pharmaceutically acceptable compositions can be formulated in a suitable lotion or cream containing the active components

suspended or dissolved in one or more pharmaceutically acceptable carriers. Suitable carriers include, but are

20 not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol,

2-octyldodecanol, benzyl alcohol and water.

For ophthalmic use, the pharmaceutically acceptable compositions may be formulated as micronized

25 suspensions in isotonic, pH adjusted sterile saline, or, preferably, as solutions in isotonic, pH adjusted sterile saline, either with or without a preservative such as benzylalkonium chloride. Alternatively, for ophthalmic uses, the pharmaceutically acceptable compositions may be

30 formulated in an ointment such as petrolatum.

The pharmaceutically acceptable compositions of this invention may also be administered by nasal aerosol or inhalation. Such compositions are prepared according

-60-

to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability,
5 fluorocarbons, and/or other conventional solubilizing or dispersing agents.

Most preferably, the pharmaceutically acceptable compositions of this invention are formulated for oral administration.

10 The amount of the compounds of the present invention that may be combined with the carrier materials to produce a composition in a single dosage form will vary depending upon the host treated, the particular mode of administration. Preferably, the compositions should
15 be formulated so that a dosage of between 0.01 - 100 mg/kg body weight/day of the inhibitor can be administered to a patient receiving these compositions.

It should also be understood that a specific dosage and treatment regimen for any particular patient
20 will depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, rate of excretion, drug combination, and the judgment of the treating physician and the severity
25 of the particular disease being treated. The amount of a compound of the present invention in the composition will also depend upon the particular compound in the composition.

Depending upon the particular condition, or
30 disease, to be treated or prevented, additional therapeutic agents, which are normally administered to treat or prevent that condition, may also be present in the compositions of this invention.

-61-

For example, chemotherapeutic agents or other anti-proliferative agents may be combined with the compounds of this invention to treat proliferative diseases and cancer. Examples of known chemotherapeutic 5 agents include, but are not limited to, Gleevec™, adriamycin, dexamethasone, vincristine, cyclophosphamide, fluorouracil, topotecan, taxol, interferons, and platinum derivatives.

Other examples of agents the compounds of this 10 invention may also be combined with include, without limitation, anti-inflammatory agents such as corticosteroids, TNF blockers, IL-1 RA, azathioprine, cyclophosphamide, and sulfasalazine; immunomodulatory and immunosuppressive agents such as cyclosporin, tacrolimus, 15 rapamycin, mycophenolate mofetil, interferons, corticosteroids, cyclophosphamide, azathioprine, and sulfasalazine; neurotrophic factors such as acetylcholinesterase inhibitors, MAO inhibitors, interferons, anti-convulsants, ion channel blockers, 20 riluzole, and anti-Parkinsonian agents; agents for treating cardiovascular disease such as beta-blockers, ACE inhibitors, diuretics, nitrates, calcium channel blockers, and statins; agents for treating liver disease such as corticosteroids, cholestyramine, interferons, and 25 anti-viral agents; agents for treating blood disorders such as corticosteroids, anti-leukemic agents, and growth factors; agents for treating diabetes such as insulin, insulin analogues, alpha glucosidase inhibitors, biguanides, and insulin sensitizers; and agents for 30 treating immunodeficiency disorders such as gamma globulin.

The amount of additional therapeutic agent present in the compositions of this invention will be no

-62-

more than the amount that would normally be administered in a composition comprising that therapeutic agent as the only active agent. Preferably the amount of additional therapeutic agent in the presently disclosed compositions 5 will range from about 50% to 100% of the amount normally present in a composition comprising that agent as the only therapeutically active agent.

According to another embodiment, the invention relates to a method of inhibiting JNK3, GSK-3, CDK2, Lck, 10 or Src kinase activity in a biological sample comprising the step of contacting said biological sample with a compound of this invention, or composition comprising said compound.

The term "biological sample", as used herein, 15 includes, without limitation, cell cultures or extracts thereof; biopsied material obtained from a mammal or extracts thereof; and blood, saliva, urine, feces, semen, tears, or other body fluids or extracts thereof.

Inhibition of JNK3, GSK-3, CDK2, Lck, or Src 20 kinase activity in a biological sample is useful for a variety of purposes which are known to one of skill in the art. Examples of such purposes include, but are not limited to, blood transfusion, organ-transplantation, biological specimen storage, and biological assays.

According to another embodiment, the invention 25 provides a method for treating or lessening the severity of a JNK3-, GSK-3-, CDK2-, Lck-, or Src-mediated disease or condition in a patient comprising the step of administering to said patient a composition according to 30 the present invention.

According to another embodiment, the present invention relates to a method of treating cancer comprising the step of blocking the transition of cancer

-63-

cells into their proliferative phase by inhibiting CDK2 with a compound according to the present invention, or a pharmaceutcially acceptable composition comprising said compound.

5 The term "JNK-mediated disease", as used herein means any disease or other deleterious condition in which JNK is known to play a role. Such conditions include, without limitation, inflammatory diseases, autoimmune diseases, destructive bone disorders, proliferative 10 disorders, cancer, infectious diseases, neurodegenerative diseases, allergies, reperfusion/ischemia in stroke, heart attacks, angiogenic disorders, organ hypoxia, vascular hyperplasia, cardiac hypertrophy, thrombin-induced platelet aggregation, and conditions associated 15 with prostaglandin endoperoxidase synthase-2.

Inflammatory diseases which may be treated or prevented by the compounds of this invention include, but are not limited to, acute pancreatitis, chronic pancreatitis, asthma, allergies, and adult respiratory 20 distress syndrome.

Autoimmune diseases which may be treated or prevented by the compounds of this invention include, but are not limited to, glomerulonephritis, rheumatoid arthritis, systemic lupus erythematosus, scleroderma, 25 chronic thyroiditis, Graves' disease, autoimmune gastritis, diabetes, autoimmune hemolytic anemia, autoimmune neutropenia, thrombocytopenia, atopic dermatitis, chronic active hepatitis, myasthenia gravis, multiple sclerosis, inflammatory bowel disease, 30 ulcerative colitis, Crohn's disease, psoriasis, or graft vs. host disease.

Destructive bone disorders which may be treated or prevented by the compounds of this invention include,

-64-

but are not limited to, osteoporosis, osteoarthritis and multiple myeloma-related bone disorder.

Proliferative diseases which may be treated or prevented by the compounds of this invention include, but 5 are not limited to, acute myelogenous leukemia, chronic myelogenous leukemia, metastatic melanoma, Kaposi's sarcoma, multiple myeloma and HTLV-1 mediated tumorigenesis.

Angiogenic disorders which may be treated or 10 prevented by the compounds of this invention include solid tumors, ocular neovascularization, infantile haemangiomas. Infectious diseases which may be treated or prevented by the compounds of this invention include, but are not limited to, sepsis, septic shock, and 15 Shigellosis.

Viral diseases which may be treated or 20 prevented by the compounds of this invention include, but are not limited to, acute hepatitis infection (including hepatitis A, hepatitis B and hepatitis C), HIV infection and CMV retinitis.

Neurodegenerative diseases which may be treated or prevented by the compounds of this invention include, but are not limited to, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis (ALS), epilepsy, 25 seizures, Huntington's disease, traumatic brain injury, ischemic and hemorrhaging stroke, cerebral ischemias or neurodegenerative disease, including apoptosis-driven neurodegenerative disease, caused by traumatic injury, acute hypoxia, ischemia or glutamate neurotoxicity.

30 "JNK-mediated diseases" also include ischemia/reperfusion in stroke, heart attacks, myocardial ischemia, organ hypoxia, vascular hyperplasia, cardiac hypertrophy, hepatic ischemia, liver disease, congestive

-65-

heart failure, pathologic immune responses such as that caused by T cell activation and thrombin-induced platelet aggregation.

In addition, compounds of the instant invention
5 may be capable of inhibiting the expression of inducible pro-inflammatory proteins. Therefore, other "JNK-mediated conditions" which may be treated by the compounds of this invention include edema, analgesia, fever and pain, such as neuromuscular pain, headache, cancer pain, dental pain
10 and arthritis pain.

The compounds of this invention are also useful as inhibitors of Src-family kinases, especially Src and Lck. For a general review of these kinases see Thomas and Brugge, *Annu. Rev. Cell Dev. Biol.* (1997) 13, 513; Lawrence and Niu, *Pharmacol. Ther.* (1998) 77, 81; Tatosyan and Mizenina, *Biochemistry (Moscow)* (2000) 65, 49. The term "Src-mediated or Lck-mediated disease", as used herein means any disease or other deleterious condition in which Src or Lck is known to play a role.
20 Accordingly, these compounds are useful for treating diseases or conditions that are known to be affected by the activity of one or more Src-family kinases. Such diseases or conditions include hypercalcemia, restenosis, osteoporosis, osteoarthritis, symptomatic treatment of
25 bone metastasis, rheumatoid arthritis, inflammatory bowel disease, multiple sclerosis, psoriasis, lupus, graft vs. host disease, T-cell mediated hypersensitivity disease, Hashimoto's thyroiditis, Guillain-Barre syndrome, chronic obstructive pulmonary disorder, contact dermatitis,
30 cancer, Paget's disease, asthma, ischemic or reperfusion injury, allergic disease, atopic dermatitis, and allergic rhinitis. Diseases that are affected by Src activity, in particular, include hypercalcemia, osteoporosis,

-66-

osteoarthritis, cancer, symptomatic treatment of bone metastasis, and Paget's disease. Diseases that are affected by Lck activity, in particular, include autoimmune diseases, allergies, rheumatoid arthritis, and 5 leukemia.

The term "GSK3-mediated disease", as used herein means any disease or other deleterious condition in which GSK3 is known to play a role. Accordingly, these compounds are useful for treating diseases or 10 conditions that are known to be affected by the activity of GSK3 kinase. Such diseases or conditions include diabetes, Alzheimer's disease, Huntington's, Parkinson's, AIDS associated dementia, amyotrophic lateral sclerosis (AML), multiple sclerosis (MS), schizophrenia, 15 cardiomyocyte hypertrophy, and baldness.

The term "CDK2-mediated disease", as used herein means any disease or other deleterious condition in which CDK2 is known to play a role. Accordingly, these compounds are useful for treating diseases or 20 conditions that are known to be affected by the activity of CDK2 kinase. Such diseases or conditions include viral infections, neurodegenerative disorders, disorders associated with thymocyte apoptosis, or proliferative disorders resulting from the deregulation of the cell 25 cycle, especially of the progression from G₁ to S phase.

A preferred embodiment relates to the method used to treat or prevent a JNK-mediated disease selected from inflammatory diseases, autoimmune diseases, destructive bone disorders, neurodegenerative diseases, 30 allergies, reperfusion/ischemia in stroke, heart attacks, angiogenic disorders, organ hypoxia, vascular hyperplasia, cardiac hypertrophy, or thrombin-induced platelet aggregation.

-67-

Another preferred embodiment relates to the method used to treat or prevent a Src- or Lck-mediated disease selected from hypercalcemia, osteoporosis, osteoarthritis, or symptomatic treatment of bone metastasis.

5 Another preferred embodiment relates to the method used to treat or prevent a GSK3-mediated disease selected from diabetes, Alzheimer's disease, Huntington's disease, Parkinson's disease, multiple sclerosis (MS), or 10 amyotrophic lateral sclerosis (AML).

According to another preferred embodiment, the method is used to treat or prevent a CDK2-mediated disease selected from viral infections, neurodegenerative disorders, or disorders associated with thymocyte 15 apoptosis.

In addition to the compounds of this invention, pharmaceutically acceptable derivatives the compounds of this invention may also be employed in compositions to treat or prevent the above-identified disorders.

20 In an alternate embodiment, the methods of this invention that utilize compositions that do not contain an additional therapeutic agent, comprise the additional step of separately administering to said patient an additional therapeutic agent. When these additional 25 therapeutic agents are administered separately they may be administered to the patient prior to, sequentially with or following administration of the compositions of this invention.

The compounds of this invention or pharmaceutical 30 compositions thereof may also be incorporated into compositions for coating an implantable medical device, such as prostheses, artificial valves, vascular grafts, stents and catheters. Vascular stents, for example, have been used to overcome

-68-

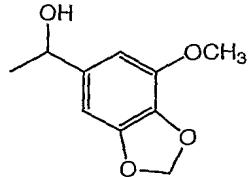
restenosis (re-narrowing of the vessel wall after injury). However, patients using stents or other implantable devices risk clot formation or platelet activation. These unwanted effects may be prevented or mitigated by pre-coating the 5 device with a pharmaceutically acceptable composition comprising a kinase inhibitor. Suitable coatings and the general preparation of coated implantable devices are described in US Patents 6,099,562; 5,886,026; and 5,304,121. The coatings are typically biocompatible polymeric materials 10 such as a hydrogel polymer, polymethyldisiloxane, polycaprolactone, polyethylene glycol, polylactic acid, ethylene vinyl acetate, and mixtures thereof. The coatings may optionally be further covered by a suitable topcoat of fluorosilicone, polysaccharides, polyethylene glycol, 15 phospholipids or combinations thereof to impart controlled release characteristics in the composition. Implantable devices coated with a compound of this invention are another embodiment of the present invention.

In order that the invention described herein 20 may be more fully understood, the following examples are set forth. It should be understood that these examples are for illustrative purposes only and are not to be construed as limiting this invention in any manner.

25

EXAMPLES

Example 1



2

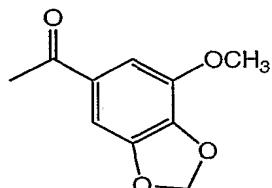
1- (7-Methoxy-benzo[1,3]dioxol-5-yl)-ethanol (2): A 30 solution of 7-Methoxy-benzo[1,3]dioxole-5-carbaldehyde

- 69 -

(I) (1.8 g, 10 mmol) in THF (20 mL) was cooled to -78°C. A solution of methylmagnesium chloride in THF (5.0 mL of 3M, 15 mmol) was added to the solution of i in THF in a dropwise fashion. The reaction was quenched by the
 5 addition of HCl (1N, aqueous) and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na₂SO₄ and concentrated *in vacuo*. The crude product was purified by flash chromatography (silica gel; 40%-60% ethyl acetate in hexanes) to afford 2 (0.89 g, 45%).

10

Example 2



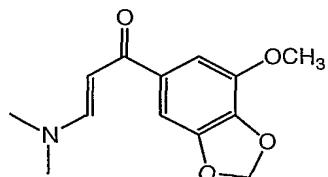
3

1- (7-Methoxy-benzo[1,3]dioxol-5-yl)-ethanone (3):

15 Manganese dioxide (5 g, molar excess) was added to a solution of 2 (0.89 g, 4.5 mmol) in dichloromethane (10 mL). The resulting mixture was heated at reflux for 3 hours then filtered through Celite®. The filtrate was concentrated *in vacuo* to afford 3 as a tan solid.

20

Example 3



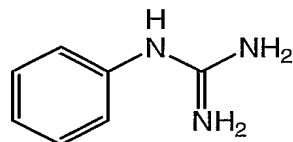
4

3-Dimethylamino-1-(7-methoxy-benzo[1,3]dioxol-5-yl)-propenone (4): A solution of 3 (0.89 g, 4.5 mmol) in N,N-dimethylformamide dimethylacetal (3.5 g, molar excess) was heated at 80°C overnight. The reaction mixture was

-70-

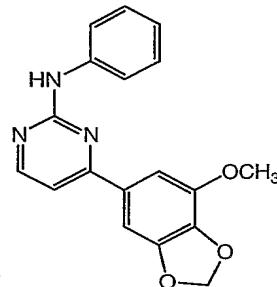
then concentrated *in vacuo* and the crude product recrystallized from ethyl acetate/hexanes to afford 4 (1.0 g, 89%).

Example 4



N-Phenyl-guanidine: A mixture of aniline (11 mmol), cyanamide (420 mg, 10 mmol), and HCl (3 mL of 4N in dioxane, 12 mmol) in 1,4-dioxane (10 mL) was heated in a sealed tube at 60°C overnight. The reaction was concentrated *in vacuo* and the residue partitioned between NaOH (2N) and dichloromethane. The organic layer was dried over Na₂SO₄ and concentrated *in vacuo* to afford N-phenyl-guanidine.

Example 5



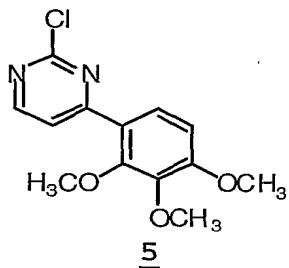
I-26

[4-(7-Methoxy-benzo[1,3]dioxol-5-yl)-pyrimidin-2-yl]-phenyl-amine (I-26): In a sealed tube, N-phenyl-guanidine (40 mg, excess) was combined with 4 (50 mg, 0.2 mmol) in acetonitrile and the mixture heated to 80°C overnight. The reaction mixture was then partitioned between water and ethyl acetate. The organic layer was washed with brine, dried over Na₂SO₄ and concentrated *in vacuo*. The

-71-

crude product was purified by flash chromatography (silica gel, 40% ethyl acetate in hexanes) to afford I-26. ¹H-NMR (CDCl₃, 500 MHz) δ 8.40 (d, 1H), 7.69 (d, 2H), 7.43 (s, 1H), 7.35 (t, 2H), 7.21 (s, 1H), 7.05 (m, 2H), 6.07 (s, 2H), 3.99 (s, 3H).

Example 6

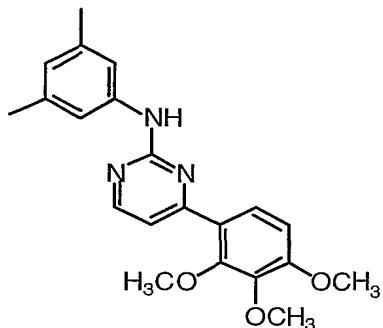


2-Chloro-4-(2,3,4-trimethoxyphenyl)pyrimidine (5): In a 250 mL round-bottomed flask, 1.49 grams (10 mmol) of 2,4-dichloropyrimidine was combined with 2,3,4-trimethoxyphenylboronic acid (2.12 g, 10 mmol), sodium carbonate (2.12 g, 2 equivalents), and 1.15 g (0.1 equivalents) of tetrakis-triphenylphosphinepalladium.

Toluene (50 mL) and water (5 mL) were added. The reaction was allowed to reflux under nitrogen overnight. The reaction was diluted with toluene and water and the organic layer was separated, washed with brine, dried (Na₂SO₄), filtered, and concentrated to afford the crude pyrimidine 5. The compound was purified on silica gel using an eluent of 30% acetone/hexane to afford 2.08 g (74%) of the product 5 as a white solid.

- 72 -

Example 7

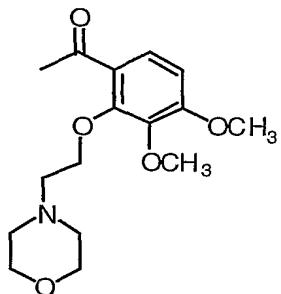


II-14

5 (3,5-Dimethylphenyl)-[4-(2,3,4-trimethoxyphenyl)-
pyrimid-2-yl]-amine (II-14): In a vial was placed 28 mg
(100 µmol) of chloropyrimidine 5, 3,5 dimethylaniline (24
mg, 200 µmol), 60% NaH (6 mg, excess), and
tetrakis(triphenylphosphine)palladium (6 mg, catalytic).
10 Tetrahydrofuran (2 mL) was added and the vial was sealed
and heated to reflux for two hours. The reaction was
diluted with diethyl ether and washed with 1N
hydrochloric acid. The organic layer was separated,
washed with 1N NaOH solution, water, and brine. The
15 organic extract was dried ($MgSO_4$), filtered, and
evaporated in vacuo to afford the crude product. The
compound was purified on silica gel using an eluent of
20% acetone/hexane to afford the pure product II-14 as a
white solid. 1H -NMR ($CDCl_3$, 500 MHz) δ 8.41 (d, 1H), 7.78
20 (d, 1H), 7.35 (d, 1H), 7.31 (s, 1H), 7.08 (s, 1H), 6.82
(d, 1H), 6.68 (s, 1H), 3.94 (s, 3H), 3.91 (s, 3H), 3.83
(s, 3H), 2.34 (s, 6H).

- 73 -

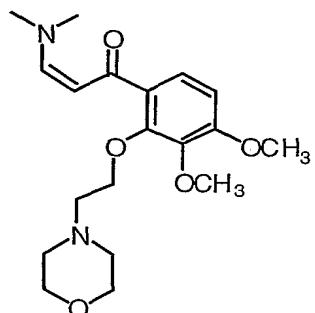
Example 8



6

1- [3,4-Dimethoxy-2- (2-morpholin-4-yl-ethoxy)phenyl-
5 ethanone (6): In a 500 mL round-bottomed flask, 2,3-
dihydroxy-4-methoxyacetophenone (3.39 grams, 17.2 mmol)
was combined with 4-(2-chloroethyl)morpholine
hydrochloride (3.53 grams, 19.0 mmol), 4 grams of K₂CO₃,
and 50 mL of anhydrous DMF. The reaction was heated to
10 60°C overnight, diluted with diethyl ether, and washed
with 1N sodium hydroxide solution. The organic layer was
washed with separated, washed with brine, dried (Na₂SO₄),
filtered, and concentrated in vacuo. The crude product
was purified by flash chromatography on silica gel using
15 an eluent of 5% MeOH-CH₂Cl₂ to afford the pure
acetophenone 6.

Example 9



20

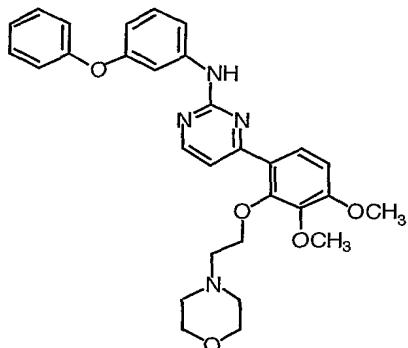
7

1- [3,4-Dimethoxy-2- (2-morpholin-4-yl-ethoxy)phenyl-3-
dimethylamino-propenone (7): In a vial, 0.95 g of 6 was

- 74 -

treated with 2 mL (excess) of dimethylformamide dimethyl acetal. The reaction was heated to 100°C overnight. The reaction was concentrated to an oil and flash-chromatographed on a silica gel column with an eluent of 5 5% MeOH/CH₂Cl₂ to afford 0.57 g (51%) of the enaminone 7.

Example 10

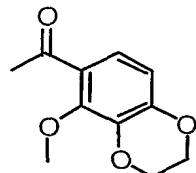


II-21

10 (4-[3,4-Dimethoxy-2-(2-morpholin-4-yl-ethoxy)phenyl-pyrimidin-2-yl]-(3-phenoxyphenyl)-amine (II-21) : In a heavy-walled screw-top glass tube, 50 mg of the enaminone 7 was combined with 3-phenoxyguanidine and 2 mL of acetonitrile. The reaction tube was sealed and heated to 15 100°C for two days. The solvent was evaporated in vacuo and the remaining material recrystallized from diethyl ether/hexane to afford pure II-21 as a white solid. ¹H-NMR (CDCl₃, 500 MHz) δ 8.32 (d, 1H), 7.62 (d, 1H), 7.60 (s, 1H), 7.48 (d, 1H), 7.32 - 7.22 (m, 5H), 7.19 (s, 1H), 20 7.09 - 7.05 (m, 2H), 6.69 - 6.63 (m, 2H), 4.05 (t, 2H), 3.94 (s, 3H), 3.91 (s, 3H), 3.68 (t, 4H), 2.62 (t, 2H), 2.42 (br s, 4H).

-75-

Example 11

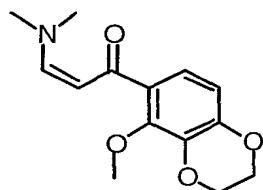


8

5 1-(5-Methoxy-2,3-dihydro-1,4-benzodioxin-6-yl)ethan-1-one
(8): In a round-bottomed flask, 500 mg of 1-(5-Hydroxy-
2,3-dihydro-1,4-benzodioxin-6-yl)ethan-1-one was
dissolved in 1 mL of DMF. To this solution was added,
414 mg of K₂CO₃, and methyl iodide (1 mL, excess). The
10 reaction was heated to 80°C overnight. The reaction was
poured into water and extracted with diethyl ether. The
organic extract was washed with brine, dried (Na₂SO₄),
filtered, and concentrated to afford 0.38 g (70%) of the
acetophenone 8.

15

Example 12

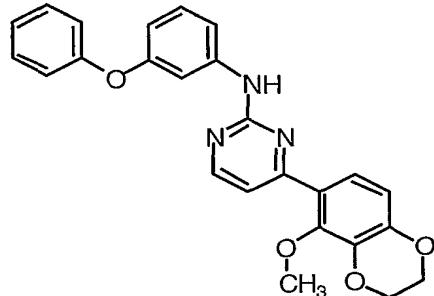


9

3-Dimethylamino-1-(5-methoxy-2,3-dihydro-
benzo[1,4]dioxin-6-yl)-propenone (9): In a vial, 0.38 g
(1.8 mmol) of 8 was dissolved in 1 mL of acetonitrile.
Dimethylformamide dimethyl acetal (321 mg, 2.7 mmol).
The vial was sealed and heated to 90°C overnight. The
reaction mixture was poured directly onto a silica gel
25 column which was then eluted with 70% ethyl
acetate/hexane. Evaporation of the appropriate fractions
afforded 0.30 g (61%) of the pure enaminone 9.

-76-

Example 13

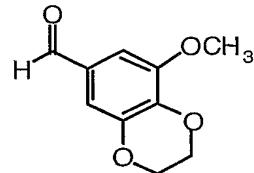


II-17

5 [4-(5-Methoxy-2,3-dihydro-benzo[1,4]dioxin-6-yl)-
pyrimidin-2-yl]- (3-phenoxyphenyl)-amine (II-17) : The
enaminone 9 was dissolved in 2 mL of acetonitrile in a
small vial. An excess of 3-phenoxyphenyl guanidine was
added, the vial was sealed, and the mixture was heated to
10 reflux overnight. The reaction mixture was poured
directly onto a silica gel column which was then eluted
with 50% ethyl acetate/hexane. The appropriate fractions
were combined and evaporated in vacuo to give the crude
pyrimidine II-17. The pyrimidine was recrystallized from
15 diethyl ether/hexane to afford pure II-17. ¹H-NMR (CDCl₃,
500 MHz) δ 9.78 (s, 1H), 8.45 (d, 1H), 7.75 (s, 1H), 7.48
(d, 1H), 7.35 (m, 2H), 7.23 (m, 3H), 7.08 (t, 1H), 6.96
(d, 2H), 6.62 (d, 1H), 6.52 (d, 1H), 4.30 (s, 4H), 3.70
(s, 3H).

20

Example 14



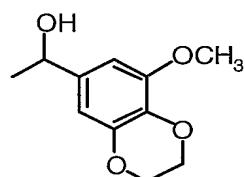
10

25 8-Methoxy-2,3-dihydro-benzo[1,4]dioxine-6-carbaldehyde
(10) : In a vial was placed 0.5 g (3.0 mmol) of 3,4-

-77-

dihydroxy-5-methoxybenzaldehyde, 414 mg (3.0 mmol) of K₂CO₃, and 3 mL of anhydrous DMF. To this mixture was added, 0.56 g (3.0 mmol) of 1,2-dibromoethane dropwise. The vial was sealed and heated to 100°C overnight. Water 5 was added to the reaction and the mixture was extracted with diethyl ether. The organic extract was washed with brine, dried (Na₂SO₄), filtered, and concentrated to give the crude product. The material was purified by silica gel chromatography using 50% ethyl acetate/hexane as the 10 eluent to afford 0.25 g (43%) of the pure aldehyde 10.

Example 15

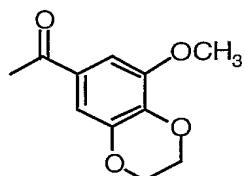


11

15 **1-(8-Methoxy-2,3-dihydro-benzo[1,4]dioxin-6-yl)-ethanol (11):** In a 250 mL round-bottomed flask, 0.60 g (3.1 mmol) of 10 was dissolved in 15 mL of anhydrous tetrahydrofuran. The solution was cooled to 0°C and treated with 1.1 mL (3.3 mmol) of 3M methyl magnesium 20 chloride in THF. The reaction was stirred for a few minutes then quenched with a 1N HCl solution. The mixture was extracted with ethyl acetate. The organic extract was washed with brine, dried (Na₂SO₄), filtered, and evaporated in vacuo to afford the alcohol 11.

25

Example 16



12

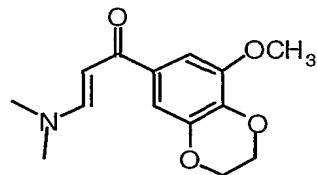
- 78 -

1-(8-Methoxy-2,3-dihydro-benzo[1,4]dioxin-6-yl)-ethanone (12):

In a round-bottomed flask, 0.65 g (3.1 mmol) of the alcohol 11 was dissolved in dichloromethane. To this solution was added an excess of manganese oxide. The suspension was heated to reflux overnight. The mixture was cooled and filtered through Celite. The filtrate was evaporated in vacuo to afford 0.61 g (85%) of 12 as a yellow oil.

10

Example 17



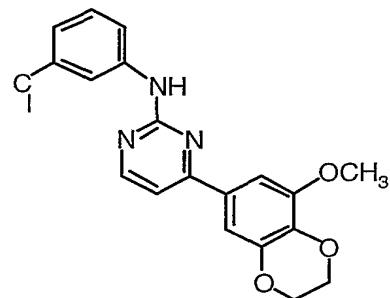
13

3-Dimethylamino-1-(8-methoxy-2,3-dihydro-

benzo[1,4]dioxin-6-yl)-propenone (13): In a vial, 548 mg

15 (2.6 mmol) of 12 was combined with 2 mL of dimethylformamide dimethyl acetal. The vial was sealed and heated to 100°C overnight. The reaction was concentrated to dryness and the crude product was recrystallized from ethyl acetate/hexane to afford 0.5 g
20 (73%) of the pure enaminone 13.

Example 18

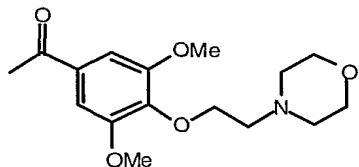


I-77

- 79 -

[4-(8-Methoxy-2,3-dihydro-benzo[1,4]dioxin-6-yl)-pyrimidin-2-yl]-(3-chlorophenyl)-amine (**I-77**): In a vial, 0.45 g (0.170 mmol) of the enaminone **13** was combined with 40 mg (excess) of 3-chlorophenyl guanidine. 5 Acetonitrile (1 mL) was added and the mixture was heated to 100°C overnight. The reaction was diluted with water and extracted with dichloromethane. The organic extract was dried (Na_2SO_4) and concentrated. The concentrated solution was poured directly onto a silica gel column 10 which was eluted with 50% ethyl acetate/hexane. The appropriate fractions were combined and evaporated in vacuo to afford the pure pyrimidine **I-77**. $^1\text{H-NMR}$ (CDCl_3 , 500 MHz) δ 8.42 (m, 1H), 8.13 (s, 1H), 7.48 (s, 1H), 7.32 – 7.20 (m, 5H), 7.10 (m, 1H), 7.0 (d, 1H), 4.49 (m, 2H), 15 4.30 (m, 2H), 4.03 (s, 3H).

Example 19

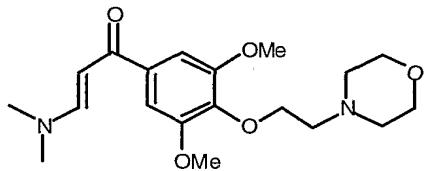


14

20 **1-[3,5-Dimethoxy-4-(2-morpholin-4-yl-ethoxy)-phenyl]ethanone (14):** In a vial, 500 mg (2.5 mmol) of 3', 5'-dimethoxy-4'-hydroxyacetophenone was combined with 4-(2-chloroethyl)morpholine hydrochloride (600 mg, 3.2 mmol), and powdered potassium carbonate (1.5 g, excess). 25 Dimethylformamide (2 mL) was added, the vial was sealed, and the rxn was heated to 80°C overnight. The reaction was diluted with water and extracted with diethyl ether. The organic extract was washed with brine, dried (Na_2SO_4), and evaporated in vacuo to afford 540 mg (67%) 30 of **14** as a white solid.

- 80 -

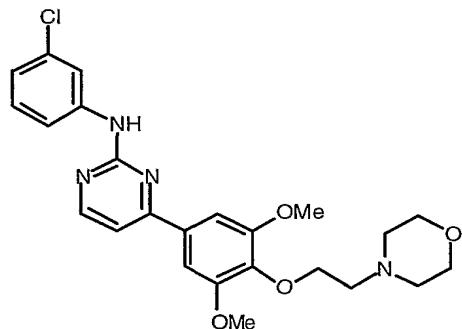
Example 20



15

5 1- [3,5-Dimethoxy-4- (2-morpholin-4-yl-ethoxy) -phenyl] -3-
dimethylamino-propenone (15) : In a vial, 540 mg (1.7
mmol) of 14 was combined with 2 mL (excess) of
dimethylformamide dimethylacetal. The reaction was
sealed and heated to 130°C overnight. The reaction was
10 concentrated to dryness and the residue was triturated
with diethyl ether/hexane to afford the pure enaminone
15.

Example 21



15

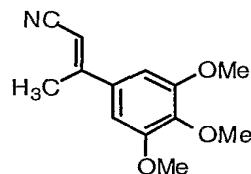
I-39

(3-Chlorophenyl) - (4 [3,5-dimethoxy-4- (2-morpholin-4-yl-ethoxy) phenyl]pyrimidin-2-yl) -amine (I-39) : In a vial,
60 mg of 3-chlorophenyl guanidine was combined with 40 mg
20 of 15. Acetonitrile (0.25 mL) was added, the vial was
sealed, and the reaction was heated to 80°C for three
days. The reaction was diluted with ethyl acetate and
washed with brine. The organic phase was separated,
dried (Na2SO4), and evaporated in vacuo. The crude

-81-

product was purified by flash chromatography on silica gel using 50% ethyl acetate/methylene chloride as the eluent to afford pure I-39. ¹H-NMR (CDCl₃, 500 MHz) δ 8.48 (d, 1H), 8.22 (s, 1H), 7.38 (s, 2H), 7.25 – 7.16 (m, 4H), 5 7.00 (d, 1H), 4.18 (br s, 2H), 3.98 (s, 6H), 3.77 (br s, 2H), 2.80 (br s, 2H), 2.59 (br s, 2H).

Example 22

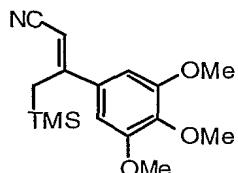


10

16

3 - (3,4,5-Trimethoxyphenyl) -but-2-enenitrile (16): To a slurry of 60% NaH (1.46 g, 61.1 mmol) in THF at 0°C was added 10.0 g (56.4 mmol) of ethyl(cyanomethyl) phosphate. 15 A solution of 9.88 g (47.0 mmol) of 3,4,5-trimethoxyacetophenone in THF was added precipitating a yellow solid. The mixture was stirred at room temperature for 30 minutes, quenched with water, and extracted with ethyl acetate. The organic extract was 20 washed with brine, dried (MgSO₄), and evaporated *in vacuo* to afford 9.32 g (85%) of 16 as a yellow oil.

Example 23



25

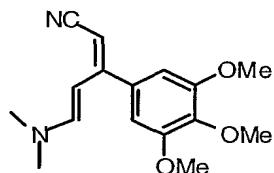
17

3 - (3,4,5) -Trimethoxyphenyl) -4 - (trimethylsilyl) -but-2- enenitrile (17): To a solution of 16 (3.82 g, 16.3 mmol)

- 82 -

in THF was added chlorotrimethylsilane (19.6 mL, 49.17 mmol). To this solution was added a solution of lithium hexamethyldisilazide in THF (24.6 mL of 1.0M, 24.6 mmol). The solution was stirred for 1 hour, quenched with water, 5 and extracted with dichloromethane. The organic extract was dried (MgSO_4), and evaporated *in vacuo* to afford a yellow oil. The oil was purified by column chromatography on silica gel using an eluent of 10-15% ethyl acetate/hexane to afford 2.6 g (52%) of 17 as a 10 white solid.

Example 24

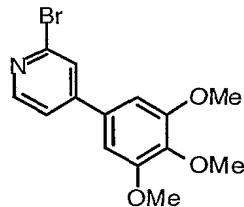


18

15 **5-Dimethylamino-3-(3,4,5-trimethoxyphenyl)penta-2,4-dienenitrile (18):** To a solution of 17 (5.8 g, 19.01 mmol) in 30 mL of toluene was added 30 mL (excess) of dimethylformamide dimethylacetal. The slurry was heated to reflux overnight. The mixture was cooled to room 20 temperature and extracted with dichloromethane. The organic extract was washed with brine, dried (MgSO_4), and evaporated *in vacuo* to afford a yellow oil. The oil was purified using column chromatography on silica gel using an eluent of 20-30% ethyl acetate/hexane to afford 3.6 g 25 (83%) of 18 as a yellow oil.

- 83 -

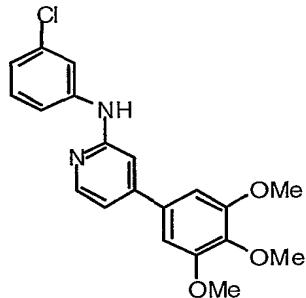
Example 25



2-Bromo-4-(3,4,5-trimethoxyphenyl)pyridine (19): Gaseous HBr was bubbled into a solution of 18 (3.6 g, 16.1 mmol) in chloroform for 15 minutes. The reaction was diluted with dichloromethane, washed with water, washed with brine, dried (MgSO_4), and evaporated *in vacuo* to afford 3.2 g (62%) of 19 as an off-white solid.

10

Example 26



I-146

(3-Chlorophenyl)-[4-(3,4,5-trimethoxyphenyl)-pyridin-2-yl]-amine (I-146): To a solution of 19 (50 mg) in 3 mL of DMF was added 2 equivalents of aniline, 2 equivalents of NaH and $\text{Pd}(\text{PPh}_3)_4$. The mixture was heated to 80°C overnight, cooled, poured into water, and extracted with ethyl acetate. The organic extract was washed with brine, dried (Na_2SO_4), and evaporated *in vacuo* to afford an brown oil. The oil was purified by prep HPLC to afford pure I-146. Expected Mass = 370.1084; Found Mass ($M+1$) = 371.0. Retention time = 3.25 minutes.

- 84 -

We have prepared other compounds of formula I by methods substantially similar to those described in the above Examples 1-26 and those illustrated in Schemes I-IV. The characterization data for these compounds is 5 summarized in Table 4 below and includes LC/MS (observed), HPLC, and ¹H NMR data.

As used herein in Table 4 below, "Y" designates the indicated data is available and was found to be consistent with structure. Compound numbers correspond 10 to the compound numbers listed in Tables 1, 2, and 3.

The term "R_t" refers to the retention time, in minutes, associated with the compound.

Table 4. Characterization Data for Selected Compounds

Compound No	M+1 (obs)	¹ H NMR	R _t
I-26	-	Y	-
I-27	-	Y	-
I-28	-	Y	-
I-29	-	Y	-
I-30	-	Y	-
I-31	-	Y	-
I-32	-	Y	-
I-33	-	Y	-
I-39	-	Y	-
I-39	Y	Y	Y
I-40	Y	Y	Y
I-41	Y	Y	Y
I-42	Y	Y	Y
I-43	Y	Y	Y
I-44	Y	Y	Y
I-45	Y	Y	Y
I-46	Y	Y	Y
I-47	Y	Y	Y
I-48	Y	Y	Y
I-49	Y	Y	Y

- 85 -

Compound No	M+1 (obs)	¹ H NMR	R _t
I-50	Y	Y	Y
I-51	Y	Y	Y
I-52	Y	Y	Y
I-53	Y	Y	Y
I-54	Y	Y	Y
I-55	Y	Y	Y
I-56	Y	-	Y
I-57	Y	-	Y
I-58	Y	-	Y
I-59	Y	-	Y
I-60	Y	-	Y
I-61	Y	-	Y
I-62	Y	-	Y
I-63	Y	-	Y
I-64	Y	-	Y
I-65	Y	-	Y
I-66	Y	-	Y
I-67	Y	-	Y
I-68	Y	-	Y
I-69	Y	-	Y
I-70	Y	-	Y
I-71	Y	-	Y
I-72	Y	-	Y
I-73	Y	-	Y
I-74	Y	Y	Y
I-75	Y	Y	Y
I-76	Y	Y	Y
I-77	Y	Y	Y
I-78	Y	Y	Y
I-79	Y	Y	Y
I-80	Y	Y	Y
I-81	Y	Y	Y
I-82	Y	Y	Y
I-83	Y	Y	Y
I-84	Y	Y	Y
I-85	Y	Y	Y

- 86 -

Compound No	M+1 (obs)	¹ H NMR	R _t
I-86	Y	Y	Y
I-87	Y	Y	Y
I-88	Y	Y	Y
I-89	Y	Y	Y
I-144	Y	-	Y
I-145	Y	-	Y
I-146	Y	-	Y
I-147	Y	-	Y
I-148	Y	-	Y
I-149	Y	-	Y
I-150	Y	-	Y
I-151	Y	-	Y
I-152	Y	-	Y
I-153	Y	-	Y
I-154	Y	-	Y
I-155	Y	-	Y
I-156	Y	-	Y
I-157	Y	-	Y
I-158	Y	-	Y
I-159	Y	-	Y
I-160	Y	-	Y
II-1	-	-	Y
II-2	-	-	Y
II-3	-	-	Y
II-4	-	-	Y
II-5	-	-	Y
II-6	-	-	Y
II-7	-	-	Y
II-8	-	-	Y
II-9	-	-	Y
II-10	-	-	Y
II-11	-	-	Y
II-12	-	-	Y
II-13	-	-	Y
II-14	Y	Y	Y
II-15	Y	Y	Y

- 87 -

Compound No	M+1 (obs)	¹ H NMR	R _t
II-16	Y	Y	Y
II-17	Y	Y	Y
II-18	Y	Y	Y
II-19	Y	Y	Y
II-20	Y	Y	Y
II-21	Y	Y	Y
II-22	Y	Y	Y
II-23	Y	-	Y
II-24	Y	-	Y
II-25	Y	-	Y
II-44	Y	-	Y
II-45	Y	-	Y
II-46	Y	-	Y
II-47	Y	-	Y
II-48	Y	-	Y
II-49	Y	-	Y
II-50	Y	-	Y
II-51	Y	-	Y
II-52	Y	-	Y
II-53	Y	-	Y
II-54	Y	-	Y
II-55	Y	-	Y
II-57	Y	-	Y
II-58	Y	-	Y
II-59	Y	-	Y
II-60	Y	-	Y
II-61	Y	-	Y
II-64	Y	-	Y
II-65	Y	-	Y
II-66	Y	-	Y
II-67	Y	-	Y
II-68	Y	-	Y
II-69	Y	-	Y

- 88 -

The following examples demonstrate how the compounds of this invention may be tested as inhibitors of JNK3, Src, Lck, GSK3, and CDK2 kinases.

5

Example 27

Cloning, Expression and Purification of JNK3 Protein

A BLAST search of the EST database using the published JNK3 α 1 cDNA as a query identified an EST clone (#632588) that contained the entire coding sequence for 10 human JNK3 α 1. Polymerase chain reactions (PCR) using *pfu* polymerase (Strategene) were used to introduce restriction sites into the cDNA for cloning into the pET-15B expression vector at the NcoI and BamHI sites. The protein was expressed in *E. coli*. Due to the poor 15 solubility of the expressed full-length protein (Met 1-Gln 422), an N-terminally truncated protein starting at Ser residue at position 40 (Ser 40) was produced. This truncation corresponds to Ser 2 of JNK1 and JNK2 proteins, and is preceded by a methionine (initiation) 20 and a glycine residue. The glycine residue was added in order to introduce an NcoI site for cloning into the expression vector. In addition, systematic C-terminal truncations were performed by PCR to identify a construct that give rise to diffraction-quality crystals. One such 25 construct encodes amino acid residues Ser40-Glu402 of JNK3 α 1 and is preceded by Met and Gly residues.

The construct was prepared by PCR using deoxyoligonucleotides:

5' GCTCTAGAGCTCCCATGGGCAGCAAAAGCAAAGTTGACAA 3' (forward 30 primer with initiation codon underlined) (SEQ ID NO:1) and 5' TAGCGGATCCTCATTCTGAATTCAATTACTCCTTGTA 3' (reverse primer with stop codon underlined) (SEQ ID NO:2) as

-89-

primers and was confirmed by DNA sequencing. Control experiments indicated that the truncated JNK3 protein had an equivalent kinase activity towards myelin basic protein when activated with an upstream kinase MKK7 *in vitro*.

5 *E.coli* strain BL21 (DE3) (Novagen) was transformed with the JNK3 expression construct and grown at 30°C in LB supplemented with 100 µg/ml carbenicillin in shaker flasks until the cells were in log phase ($OD_{600} \sim 0.8$). 10 Isopropylthio- β -D-galactosidase (IPTG) was added to a final concentration of 0.8 mM and the cells were harvested 2 hours later by centrifugation.

15 *E. coli* cell paste containing JNK3 was resuspended in 10 volumes/g lysis buffer (50 mM HEPES, pH 7.2, containing 10% glycerol (v/v), 100 mM NaCl, 2 mM DTT, 0.1 mM PMSF, 2 µg/ml Pepstatin, 1µg/ml each of E-64 and Leupeptin). Cells were lysed on ice using a microfluidizer and centrifuged at 100,000 $\times g$ for 30 min at 4 °C. The 100,000 $\times g$ supernatant was diluted 1:5 20 with Buffer A (20 mM HEPES, pH 7.0, 10% glycerol (v/v), 2 mM DTT) and purified by SP-Sepharose (Pharmacia) cation-exchange chromatography (column dimensions: 2.6 x 20 cm) at 4 °C. The resin was washed with 5 column volumes of Buffer A, followed by 5 column volumes of Buffer A 25 containing 50 mM NaCl. Bound JNK3 was eluted with a 7.5 column volume linear gradient of 50-300 mM NaCl. JNK3 eluted between 150-200 mM NaCl.

Example 28

30 Activation of JNK3

5 mg of JNK3 was diluted to 0.5 mg/ml in 50 mM HEPES buffer, pH 7.5, containing 100 mM NaCl, 5 mM DTT, 20 mM MgCl₂ and 1 mM ATP. GST-MKK7(DD) was added at a

-90-

molar ratio of 1:2.5 GST-MKK7:JNK3. After incubation for 30 minutes at 25°C, the reaction mixture was concentrated 5-fold by ultrafiltration in a Centriprep-30 (Amicon, Beverly, MA), diluted to 10 ml and an additional 1 mM ATP added. This procedure was repeated three times to remove ADP and replenish ATP. The final addition of ATP was 5 mM and the mixture incubated overnight at 4°C.

The activated JNK3/GST-MKK7 (DD) reaction mixture was exchanged into 50 mM HEPES buffer, pH 7.5, containing 5 mM DTT and 5% glycerol (w/v) by dialysis or ultrafiltration. The reaction mixture was adjusted to 1.1 M potassium phosphate, pH 7.5, and purified by hydrophobic interaction chromatography (at 25 °C) using a Rainin Hydropore column. GST-MKK7 and unactivated JNK3 do not bind under these conditions such that when a 1.1 to 0.05 M potassium phosphate gradient is developed over 60 minutes at a flow rate of 1 ml/minute, doubly phosphorylated JNK3 is separated from singly phosphorylated JNK. Activated JNK3 (i.e. doubly phosphorylated JNK3) was stored at -70°C at 0.25-1 mg/ml.

Example 29

JNK Inhibition Assay

Compounds were assayed for the inhibition of JNK3 by a spectrophotometric coupled-enzyme assay. In this assay, a fixed concentration of activated JNK3 (10 nM) was incubated with various concentrations of a potential inhibitor dissolved in DMSO for 10 minutes at 30°C in a buffer containing 0.1 M HEPES buffer, pH 7.5, containing 10 mM MgCl₂, 2.5 mM phosphoenolpyruvate, 200 μM NADH, 150 μg/mL pyruvate kinase, 50 μg/mL lactate dehydrogenase, and 200 μM EGF receptor peptide. The EGF receptor peptide has the sequence KRELVEPLTPSGEAPNQALLR,

-91-

and is a phosphoryl acceptor in the JNK3-catalyzed kinase reaction. The reaction was initiated by the addition of 10 μ M ATP and the assay plate is inserted into the spectrophotometer's assay plate compartment that was 5 maintained at 30°C. The decrease of absorbance at 340 nm was monitored as a function of time. The rate data as a function of inhibitor concentration was fitted to competitive inhibition kinetic model to determine the K_i .

Table 5 shows the results of the activity of 10 selected compounds of this invention in the JNK inhibition assay. The compound numbers correspond to the compound numbers in Tables 1, 2, and 3. Compounds having a K_i less than 0.1 micromolar (μ M) are rated "A", compounds having a K_i between 0.1 and 1 μ M are rated "B" 15 and compounds having a K_i greater than 1 μ M are rated "C". Activity ratings "D", "E", and "F" correspond to percent inhibition at a 2 μ M inhibitor concentration. Compounds having an activity designated as "D" provided a percent inhibition less than or equal to 33%; compounds having an 20 activity designated as "E" provided a percent inhibition of between 24% and 66%; and compounds having an activity designated as "F" provided a percent inhibition of between 67% and 100%.

Table 5. Activity in the JNK3 Inhibition Assay.

No.	Activity	No.	Activity	No.	Activity
I-1	B	I-2	B	I-3	A
I-4	B	I-5	B	I-6	A
I-7	B	I-8	C	I-9	A
I-10	B	I-11	A	I-12	A
I-13	A	I-14	C	I-15	A
I-16	A	I-17	A	I-18	A
I-19	A	I-20	A	I-21	A

- 92 -

No.	Activity	No.	Activity	No.	Activity
I-22	A	I-23	A	I-24	B
I-25	A	I-26	B	I-27	C
I-28	B	I-29	B	I-30	C
I-31	C	I-32	B	I-33	B
I-34	A	I-35	A	I-36	A
I-37	C	I-38	A	I-39	A
I-40	A	I-41	B	I-42	A
I-43	B	I-44	A	I-45	A
I-46	B	I-47	A	I-48	B
I-49	A	I-50	A	I-51	A
I-52	A	I-53	A	I-54	A
I-55	A	I-56	C	I-57	A
I-58	A	I-59	A	I-60	A
I-61	A	I-62	A	I-63	A
I-64	F	I-65	D	I-66	A
I-67	D	I-68	E	I-69	D
I-70	E	I-71	D	I-72	E
I-73	A	I-74	A	I-75	A
I-76	A	I-77	A	I-78	A
I-79	A	I-80	A	I-81	A
I-82	A	I-83	C	I-84	C
I-85	B	I-86	C	I-87	B
I-88	B	I-89	B	I-94	A
I-146	B	I-147	B	I-151	B
I-154	B	I-155	B	II-32	A
II-33	C	-	-	-	-

Example 30Src Inhibition Assay

The compounds were assayed as inhibitors of full length recombinant human Src kinase (from Upstate Biotechnology, cat. no. 14-117) expressed and purified from baculo viral cells. Src kinase activity was monitored by following the incorporation of ³³P from ATP into the tyrosine of a random poly Glu-Tyr polymer

- 93 -

substrate of composition, Glu:Tyr = 4:1 (Sigma, cat. no. P-0275). The following were the final concentrations of the assay components: 0.05 M HEPES, pH 7.6, 10 mM MgCl₂, 2 mM DTT, 0.25 mg/ml BSA, 10 µM ATP (1-2 µCi ³³P-ATP per reaction), 5 mg/ml poly Glu-Tyr, and 1-2 units of recombinant human Src kinase. In a typical assay, all the reaction components with the exception of ATP were pre-mixed and aliquoted into assay plate wells.

Inhibitors dissolved in DMSO were added to the wells to give a final DMSO concentration of 2.5%. The assay plate was incubated at 30 °C for 10 min before initiating the reaction with ³³P-ATP. After 20 min of reaction, the reactions were quenched with 150 µl of 10% trichloroacetic acid (TCA) containing 20 mM Na₃PO₄. The quenched samples were then transferred to a 96-well filter plate (Whatman, UNI-Filter GF/F Glass Fiber Filter, cat no. 7700-3310) installed on a filter plate vacuum manifold. Filter plates were washed four times with 10% TCA containing 20 mM Na₃PO₄ and then 4 times with methanol. 200µl of scintillation fluid was then added to each well. The plates were sealed and the amount of radioactivity associated with the filters was quantified on a TopCount scintillation counter.

Table 6 shows the results of the activity of selected compounds of this invention in the SRC inhibition assay. The compound numbers correspond to the compound numbers in Tables 1, 2, and 3. Compounds having a K_i less than 0.1 micromolar (µM) are rated "A", compounds having a K_i between 0.1 and 1 µM are rated "B" and compounds having a K_i greater than 1 µM are rated "C". Activity ratings "D", "E", and "F" correspond to percent inhibition at a 2 µM inhibitor concentration. Compounds

-94-

having an activity designated as "D" provided a percent inhibition less than or equal to 33%; compounds having an activity designated as "E" provided a percent inhibition of between 24% and 66%; and compounds having an activity 5 designated as "F" provided a provided a percent inhibition of between 67% and 100%.

Table 6. Activity in the SRC Inhibition Assay.

No.	Activity	No.	Activity	No.	Activity
I-1	C	I-3	D	I-4	C
I-12	D	I-13	E	I-34	C
I-48	E	I-50	F	I-57	E
I-58	E	I-59	F	I-60	F
I-61	D	I-62	D	I-63	E
I-64	F	I-67	D	I-68	D
I-69	D	I-70	D	I-71	D
I-72	D	I-73	E	I-74	E
I-75	F	I-76	E	I-77	F
I-78	E	I-79	E	I-80	E
I-81	F	I-82	D	II-1	A
II-24	A	II-62	B	II-63	A
II-64	A	II-65	B	II-66	C
II-67	A	II-68	B	II-69	A

10

Example 31

Lck Inhibition Assay

The compounds were assayed as inhibitors of Lck kinase purified from bovine thymus (from Upstate Biotechnology, cat. no. 14-106). Lck kinase activity was 15 monitored by following the incorporation of ^{33}P from ATP into the tyrosine of a random poly Glu-Tyr polymer substrate of composition, Glu:Tyr = 4:1 (Sigma, cat. no. P-0275). The following were the final concentrations of the assay components: 0.05 M HEPES, pH 7.6, 10 mM MgCl₂, 2 mM DTT, 0.25 mg/ml BSA, 10 μM ATP (1-2 μCi ^{33}P -ATP per 20

-95-

reaction), 5 mg/ml poly Glu-Tyr, and 1-2 units of lck kinase. In a typical assay, all the reaction components with the exception of ATP were pre-mixed and aliquoted into assay plate wells. Inhibitors dissolved in DMSO 5 were added to the wells to give a final DMSO concentration of 2.5%. The assay plate was incubated at 30 °C for 10 min before initiating the reaction with ³³P-ATP. After 20 min of reaction, the reactions were quenched with 150 µl of 10% trichloroacetic acid (TCA) 10 containing 20 mM Na₃PO₄. The quenched samples were then transferred to a 96-well filter plate (Whatman, UNI-Filter GF/F Glass Fiber Filter, cat no. 7700-3310) installed on a filter plate vacuum manifold . Filter plates were washed four times with 10% TCA containing 20 mM Na₃PO₄ and then 4 times with methanol. 200µl of scintillation fluid was then added to each well. The plates were sealed and the amount of radioactivity associated with the filters was quantified on a TopCount 15 scintillation counter.

Table 7 shows the results of the activity of selected compounds of this invention in the Lck inhibition assay. The compound numbers correspond to the compound numbers in Tables 1, 2, and 3. Compounds having a K_i less than 0.1 micromolar (µM) are rated "A", 20 compounds having a K_i between 0.1 and 1 µM are rated "B" and compounds having a K_i greater than 1 µM are rated "C". Activity ratings "D", "E", and "F" correspond to percent inhibition at a 5 µM inhibitor concentration. Compounds having an activity designated as "D" provided a percent 25 inhibition less than or equal to 33%; compounds having an activity designated as "E" provided a percent inhibition of between 24% and 66%; and compounds having an activity 30

- 96 -

designated as "F" provided a provided a percent inhibition of between 67% and 100%.

Table 7. Activity in the Lck Inhibition Assay.

No.	Activity	No.	Activity	No.	Activity
I-3	C	I-34	C	I-57	B
I-66	E	I-68	D	I-85	B
I-89	B	I-94	B	-	-
II-1	A	II-2	B	II-3	D
II-4	B	II-5	C	II-6	B
II-7	E	II-8	E	II-9	D
II-10	C	II-11	E	II-12	B
II-14	F	II-15	B	II-16	B
II-17	C	II-18	C	II-19	C
II-20	C	II-21	C	II-22	C
II-23	A	II-24	B	II-25	A
II-26	A	II-27	B	II-31	A
II-32	C	II-33	C	II-34	C
II-35	A	II-36	A	II-37	A
II-38	B	II-39	A	II-40	A
II-41	B	II-42	B	II-43	A
II-44	B	II-45	B	II-46	B
II-47	B	II-48	B	II-49	A
II-50	B	II-51	B	II-52	B
II-53	B	II-54	B	II-55	A
II-57	C	II-58	C	II-59	B
II-60	B	II-61	B	II-62	C
II-63	B	II-70	B	II-71	B
II-72	C	II-73	A	II-74	A
II-75	A	II-76	A	-	-

5

Example 32

GSK-3 Inhibition Assay

Compounds were screened in the following manner
 for their ability to inhibit Glycogen Synthase Kinase 3
 10 (GSK-3) using a standard coupled enzyme assay (Fox et al

- 97 -

(1998) *Protein Sci* 7, 2249). To an assay stock buffer solution containing 0.1M HEPES 7.5, 10 mM MgCl₂, 25 mM NaCl, 2.5 mM phosphoenolpyruvate, 300 µM NADH, 1mM DTT, 30 µg/mL pyruvate kinase, 10 µg/mL lactate dehydrogenase, 5 300 µM peptide (HSSPHQp-SEDEEE, American Peptide, Sunnyvale, CA), and 60 nM GSK-3, was added a 30 µM solution of the compound in DMSO and the resulting mixture incubated at 30°C for 5 min. The reaction was initiated by the addition of 10 µM ATP. The rates of 10 reaction were obtained by monitoring absorbance at 340 nM over a 5 minute read time at 30°C using a Molecular Devices plate reader (Sunnyvale, CA). The IC₅₀ was determined from the rate data as a function of inhibitor concentration.

15 Table 8 shows the results of the activity of selected compounds of this invention in the GSK-3 inhibition assay. The compound numbers correspond to the compound numbers in Tables 1, 2, and 3. Compounds having a K_i less than 0.1 micromolar (µM) are rated "A", 20 compounds having a K_i between 0.1 and 1 µM are rated "B" and compounds having a K_i greater than 1 µM are rated "C".

Table 8. GSK-3 Inhibitory Activity of Selected Compounds

No.	Activity	No.	Activity	No.	Activity
I-1	C	I-3	F	I-4	C
I-5	C	I-9	B	I-10	B
I-12	B	I-18	A	I-20	B
I-22	C	I-34	B	I-35	A
I-37	C	I-38	A	I-39	B
I-41	B	I-42	C	I-43	B
I-48	B	I-49	B	I-50	E
I-51	B	I-52	B	I-57	B
I-59	A	I-62	B	I-64	B

-98-

No.	Activity	No.	Activity	No.	Activity
I-65	A	I-66	A	I-68	E
I-75	A	I-83	C	I-87	C
I-88	C	I-158	C	I-159	B
I-160	C	II-18	C	II-25	A
II-26	A	II-32	B	II-33	C
II-44	C	II-45	C	II-46	C
II-47	B	II-48	B	II-64	C
II-65	C	II-66	C	II-67	A
II-68	A	II-69	A	II-70	B
II-71	C	II-72	C	II-73	A
II-74	A	II-75	A	II-76	B

Example 33

CDK2 Inhibition Assay

Compounds were screened in the following manner
 5 for their ability to inhibit CDK2 using a standard coupled enzyme assay (Fox et al (1998) *Protein Sci* 7, 2249).

To an assay stock buffer solution containing 0.1M HEPES 7.5, 10 mM MgCl₂, 1 mM DTT, 25 mM NaCl, 2.5 mM phosphoenolpyruvate, 300 mM NADH, 30 mg/ml pyruvate kinase, 10 mg/ml lactate dehydrogenase, 100 mM ATP, and 100 μM peptide (MAHHHRSPRKRAKKK, American Peptide, Sunnyvale, CA) was added a DMSO solution of a compound of the present invention to a final concentration of 30 μM.
 15 The resulting mixture was incubated at 30 °C for 10 minutes.

The reaction was initiated by the addition of 10 μL of CDK-2/Cyclin A stock solution to give a final concentration of 25 nM in the assay. The rates of reaction were obtained by monitoring absorbance at 340 nm over a 5-minute read time at 30 °C using a BioRad Ultramark plate reader (Hercules, CA). The K_i values were

-99-

determined from the rate data as a function of inhibitor concentration.

Table 9 shows the results of the activity of selected compounds of this invention in the CDK2 inhibition assay. The compound numbers correspond to the compound numbers in Tables 1, 2, and 3. Compounds having a K_i less than 2 micromolar (μM) are rated "A", compounds having a K_i between 2 and 5 μM are rated "B" and compounds having a K_i greater than 5 μM are rated "C".

10

Table 9. CDK2 Inhibitory Activity of Selected Compounds

No.	Activity	No.	Activity	No.	Activity
I-1	C	I-2	C	I-3	C
I-4	C	I-5	C	I-6	C
I-7	C	I-8	C	I-9	C
I-10	C	I-11	C	I-12	C
I-13	C	I-15	C	I-16	C
I-18	C	I-19	C	I-20	C
I-21	C	I-22	C	I-23	C
I-24	C	I-26	C	I-32	C
I-33	C	I-34	C	I-35	C
I-36	C	I-38	C	I-39	C
I-40	C	I-41	C	I-42	C
I-43	C	I-44	C	I-45	C
I-46	C	I-49	C	I-51	C
I-53	C	I-54	C	I-55	C
I-56	C	I-57	C	I-59	C
I-60	C	I-61	C	I-65	C
I-66	A	I-68	B	II-44	C
II-45	C	II-46	C	II-47	C
II-48	C	II-49	C	II-50	C
II-51	C	II-52	C	II-53	C
II-54	C	II-55	C	II-56	C
II-57	C	II-58	C	II-59	C
II-60	C	II-61	C	II-62	C

-100-

No.	Activity	No.	Activity	No.	Activity
II-70	C	II-71	C	II-72	C
II-73	C	II-74	C	II-75	C
II-76	C				

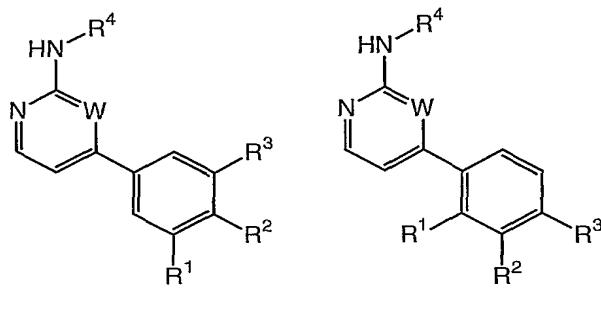
While we have described a number of embodiments of this invention, it is apparent that our basic examples may be altered to provide other embodiments which utilize 5 the compounds and methods of this invention. Therefore, it will be appreciated that the scope of this invention is to be defined by the appended claims rather than by the specific embodiments which have been represented by way of example.

-101-

CLAIMS

We claim:

1. A compound of formula I or II:



or a pharmaceutically acceptable derivative thereof,
wherein:

each W is independently selected from nitrogen or CH;

each R¹, R², and R³ is independently selected from

halogen, QR, Q_(n)CN, Q_(n)NO₂, or Q_(n)Ar²; wherein:

R¹ and R² or R² and R³ are optionally taken together
to form a 4-8 membered saturated, partially
unsaturated, or fully unsaturated ring having 0-3
heteroatoms independently selected from nitrogen,
oxygen, or sulfur;

n is zero or one;

Q is a C₁₋₄ alkylidene chain wherein one methylene unit of

Q is optionally replaced by O, S, NR, NRCO, NRCONR,
NRCO₂, CO, CO₂, CONR, OC(O)NR, SO₂, SO₂NR, NRSO₂,
NRSO₂NR, C(O)C(O), or C(O)CH₂C(O);

each R is independently selected from hydrogen or an
optionally substituted C_{1-C4} aliphatic, wherein:

two R bound to the same nitrogen atom are optionally
taken together with the nitrogen atom to form a 3-
7 membered saturated, partially unsaturated, or
fully unsaturated ring having 1-2 additional

-102-

heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R^4 is Ar^1 , $T-Ar^2$, or $T_{(n)}-Ar^3$;

T is a C_{1-2} alkylidene chain wherein one methylene unit of T is optionally replaced by O, NR, NRCO, NRCONR, NRCO₂, CO, CO₂, CONR, OC(O)NR, SO₂, SO₂NR, NRSO₂, NRSO₂NR, C(O)C(O), or C(O)CH₂C(O);

Ar^1 is a 5-6 membered monocyclic or 8-10 membered bicyclic saturated, partially unsaturated, or fully unsaturated ring system; wherein:

Ar^1 is optionally substituted with up to five substituents, wherein the first substituent is selected from R^x or R^5 and wherein any additional substituents are independently selected from R^5 ;

each R^x is independently selected from a 5-6 membered aryl ring having 0-3 heteroatoms selected from nitrogen, oxygen, or sulfur, wherein:

R^x is optionally substituted with 1-3 R^5 ;

each R^5 is independently selected from R, halogen, NO₂, CN, OR, SR, N(R)₂, NRC(O)R, NRC(O)N(R)₂, NRCO₂R, C(O)R, CO₂R, C(O)N(R)₂, OC(O)N(R)₂, SOR, SO₂R, SO₂N(R)₂, NRSO₂R, NRSO₂N(R)₂, C(O)C(O)R, or C(O)CH₂C(O)R;

Ar^2 is a 5-6 membered saturated, partially unsaturated, or fully unsaturated monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered saturated, partially unsaturated, or fully unsaturated bicyclic ring system having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; wherein:

Ar^2 is optionally substituted with up to five substituents, wherein the first substituent is selected from R^x or R^5 and wherein any additional substituents are independently selected from R^5 ;

-103-

Ar^3 is a 6-membered aryl ring having 0-2 nitrogens, wherein:

Ar^3 is substituted with one $\text{Z}-\text{R}^6$ group and optionally substituted with 1-3 R^5 ;

Z is a C_1-C_6 alkylidene chain wherein up to two non-adjacent methylene units of Z are optionally replaced by CO , CO_2 , COCO , CONR , OCONR , NRNR , NRNRCO , NRCO , NRCO_2 , NRCONR , SO , SO_2 , NRSO_2 , SO_2NR , NRSO_2NR , O , S , or NR ; and

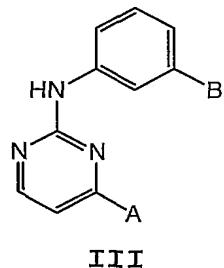
R^6 is selected from Ar^2 , R , halogen, NO_2 , CN , OR , SR , $\text{N}(\text{R})_2$, NRC(O)R , $\text{NRC(O)N}(\text{R})_2$, NRCO_2R , C(O)R , CO_2R , OC(O)R , $\text{C(O)N}(\text{R})_2$, $\text{OC(O)N}(\text{R})_2$, SOR , SO_2R , $\text{SO}_2\text{N}(\text{R})_2$, NRSO_2R , $\text{NRSO}_2\text{N}(\text{R})_2$, C(O)C(O)R , or $\text{C(O)CH}_2\text{C(O)R}$;

provided that:

(i) when R^4 is phenyl substituted with two OR , wherein R is not hydrogen, the two OR occupy positions on the phenyl ring other than simultaneously meta and para; and

(ii) said compound is other than a compound of formula

III



III

wherein:

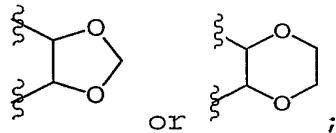
A is a phenyl ring substituted with one or more groups selected from halogen, CN , OC(O)NH_2 , CO_2R^{10} , COR^{10} , $\text{SO}_2\text{N}(\text{R}^{10})_2$, $\text{N}(\text{R}^{10})_2$, OR^{10} , or fluoro-alkyl, wherein each R^{10} is independently selected from hydrogen or a C_1-C_7 alkyl group optionally substituted with NH_2 , $\text{NH}(\text{C}_1-\text{C}_7\text{ alkyl})$, or $\text{N}(\text{C}_1-\text{C}_7\text{ alkyl})_2$; and

-104-

B is selected from halogen, CN, OC(O)NH₂, CO₂R¹⁰, COR¹⁰, SO₂N(R¹⁰)₂, N(R¹⁰)₂, OR¹⁰, or fluoro-(C₁-C₇ alkyl).

2. The compound according to claim 1, wherein:
R¹, R², and R³ are independently selected from halogen, QR or QAr²;
Q is a C₁₋₃ alkylidene chain wherein one methylene unit of Q is optionally replaced by -O-, -S-, -NHCO-, or -NR-; and
Ar² is an optionally substituted 5-6 membered saturated, partially unsaturated, or fully unsaturated ring having 0-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

3. The compound according to claim 2, wherein:
R¹, R², and R³ are independently selected from OH, OCH₃, OCH₂CH₃, NHCOMe, NH₂, NH(C₁₋₄ aliphatic), N(C₁₋₄ aliphatic)₂, O(CH₂)₂morpholin-4-yl, O(CH₂)₂NH₂, O(CH₂)₂NH(C₁₋₄ aliphatic), O(CH₂)₂N(C₁₋₄ aliphatic)₂, bromo, chloro, or fluoro; or
R¹ and R² or R² and R³ are taken together to form



and

Ar² is selected from morpholin-4-yl, pyrrolidin-1-yl, piperidin-1-yl, thiomorpholin-4-yl, pyrazol-1-yl, or imidazol-1-yl.

4. The compound according to claim 1, wherein:
R⁴ is selected from:

-105-

- (a) an optionally substituted 6-membered saturated, partially unsaturated, or aryl ring having 0-3 nitrogens;
- (b) an optionally substituted 9-10 membered bicyclic aryl ring having 0-2 nitrogens; or
- (c) an optionally substituted 5 membered heteroaryl ring having 2-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

5. The compound according to claim 4, wherein said ring is substituted with 1-3 groups independently selected from R^x, R, halogen, NO₂, OR, N(R)₂, or Z-R⁶.

6. The compound according to claim 5, wherein R^x is selected from a phenyl, pyridyl, or pyrimidinyl ring optionally substituted with 1-2 R⁵.

7. The compound according to claim 5, wherein Z is a C₁₋₄ alkylidene chain wherein one methylene unit of Z is optionally replaced by -O-, -S-, -SO₂-, or -NH-.

8. The compound according to claim 4, wherein said ring is selected from a substituted phenyl, cyclohexyl, naphthyl, pyridyl, pyrimidinyl, triazinyl, thiazolyl, thiadiazolyl, pyrazolyl, isoxazolyl, indazolyl, or benzimidazolyl ring.

9. The compound according to claim 8, wherein said ring is optionally substituted with 1-2 groups independently selected from chloro, fluoro, bromo, methyl, ethyl, t-butyl, isopropyl, cyclopropyl, nitro, OMe, OEt, CF₃, NH₂, benzyl, benzyloxy, OH, methylene dioxy, SO₂NH₂, phenoxy, O-pyridinyl, SO₂phenyl,

-106-

nitrophenoxy, aminophenoxy, S-dimethylpyrimidine, NHphenyl, NH-methoxyphenyl, pyridinyl, aminophenyl, phenol, chloro-fluoro-phenyl, dimethylaminophenyl, CF₃-phenyl, dimethylphenyl, chlorophenyl, fluorophenyl, methoxyphenoxy, chlorophenoxy, ethoxyphenoxy, or fluorophenoxy.

10. A compound selected from those listed in any of Tables 1 through 3.

11. A composition comprising a compound according to any of claims 1-10 and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

12. The composition according to claim 11, additionally comprising an additional therapeutic agent selected from an anti-proliferative agent, an anti-inflammatory agent, an immunomodulatory agent, a neurotrophic factor, an agent for treating cardiovascular disease, an agent for treating liver disease, an anti-viral agent, an agent for treating blood disorders, an agent for treating diabetes, or an agent for treating immunodeficiency disorders.

13. A method of inhibiting JNK3, GSK-3, CDK2, Lck, or Src kinase activity in a biological sample comprising the step of contacting said biological sample with:

- a) a compound according to claim 1; or
- b) a composition according to claim 11.

14. A method of treating or lessening the severity of a JNK3-, GSK-3-, CDK2-, Lck-, or Src-mediated disease or condition in a patient comprising the step of

-107-

administering to said patient a composition according to claim 11.

15. A method of treating or lessening the severity of a disease or condition in a patient selected from an inflammatory disease, autoimmune disease, destructive bone disorder, neurodegenerative disease, reperfusion/ischemia in stroke, heart attack, angiogenic disorder, organ hypoxia, vascular hyperplasia, cardiac hypertrophy, thrombin-induced platelet aggregation or a condition associated with proinflammatory cytokines, comprising the step of administering to said patient a composition according to claim 11.

16. A method of treating or lessening the severity of a disease or condition in a patient selected from selected from hypercalcemia, osteoporosis, osteoarthritis, symptomatic treatment of bone metastasis, rheumatoid arthritis, inflammatory bowel disease, multiple sclerosis, psoriasis, lupus, graft vs. host disease, T-cell mediated hypersensitivity disease, Hashimoto's thyroiditis, Guillain-Barre syndrome, chronic obstructive pulmonary disorder, contact dermatitis, Paget's disease, asthma, ischemic or reperfusion injury, allergic disease, atopic dermatitis, or allergic rhinitis, comprising the step of administering to said patient a composition according to claim 11.

17. A method of treating or lessening the severity of a disease or condition in a patient selected from diabetes, Alzheimer's disease, Huntington's, Parkinson's, AIDS associated dementia, amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), schizophrenia,

-108-

cardiomycete hypertrophy, or baldness, comprising the step of administering to said patient a composition according to claim 11.

18. A method of treating or lessening the severity of a cancer comprising the step of blocking the transition of cancer cells into their proliferative phase by inhibiting CDK2 with:

- a) a compound according to claim 1; or
- b) a composition according to claim 11.

19. The method according to claim 14, comprising the additional step of administering to said patient an additional therapeutic agent selected from an anti-proliferative agent, an anti-inflammatory agent, an immunomodulatory agent, a neurotrophic factor, an agent for treating cardiovascular disease, an agent for treating liver disease, an anti-viral agent, an agent for treating blood disorders, an agent for treating diabetes, or an agent for treating immunodeficiency disorders, wherein:

said additional therapeutic agent is appropriate for the disease being treated; and

said additional therapeutic agent is administered together with said composition as a single dosage form or separately from said composition as part of a multiple dosage form.

20. A composition for coating an implantable device comprising a compound according to claim 1 and a carrier suitable for coating said implantable device.

-109-

21. An implantable device coated with a composition according to claim 20.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 02/09554

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D405/04 A61K31/506 C07D239/42 C07D213/74 A61K31/4418
 A61P25/00 A61P37/00 A61P9/00 A61P29/00 C07D417/04
 C07D403/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

WPI Data, PAJ, EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 02 46171 A (SIGNAL PHARM INC) 13 June 2002 (2002-06-13) claim 7 ----	1-20
E	WO 02 46170 A (SIGNAL PHARM INC) 13 June 2002 (2002-06-13) claim 1 ----	1-20
P, X	WO 02 20495 A (CHIRON CORP) 14 March 2002 (2002-03-14) claims 19,37 ----	1-20
P, X	WO 01 29009 A (CELLTECH CHIROSCIENCE LTD ;DAVIS JEREMY MARTIN (GB); MOFFAT DAVID) 26 April 2001 (2001-04-26) claim 4 ----	1-20 -/-

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

° Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

Date of mailing of the international search report

9 July 2002

17/07/2002

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
 Fax: (+31-70) 340-3016

Authorized officer

Gettins, M

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 02/09554

Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 19065 A (CELLTECH THERAPEUTICS LTD ;DAVIS PETER DAVID (GB); MOFFAT DAVID FE) 29 May 1997 (1997-05-29) claims 1,8 ---	1-20
X	WO 95 09847 A (CIBA GEIGY AG ;ZIMMERMANN JUERG (CH)) 13 April 1995 (1995-04-13) See claim 6, page 60, line 23 claim 1 -----	1

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 21

Present claims 1--21 relate to an extremely large number of possible products due to the term "pharmaceutically acceptable derivative". In fact, the claims contain so many, possible permutations that a lack of clarity (and/or conciseness) within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. Additionally there does not appear to be a clear definition in the application as to what is meant to be covered by the said term. Consequently, the search has been carried out for those parts of the application which do appear to be clear i.e. the compounds of formula I or II, but NOT the pharmaceutically acceptable derivatives thereof.

Present claim 21 relates to a specifically modified (specific coating) form of every possible implantable device. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT does not appear to be present for any of the implantable devices claimed. Additionally, the claims contain so many options that a lack of clarity (and/or conciseness) within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. Consequently, the search has been carried out for those parts of the application which do appear to be clear. This means that claim 21 has not been searched.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORTInternational application No.
PCT/US 02/09554**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 13–19 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.: 21
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

Inte nal Application No
PCT/US 02/09554

Patent document cited in search report		Publication date		Patent family member(s)		Publication date
WO 0246171	A	13-06-2002	WO	0246171 A2		13-06-2002
WO 0246170	A	13-06-2002	WO	0246170 A2		13-06-2002
WO 0220495	A	14-03-2002	WO	0220495 A2		14-03-2002
WO 0129009	A	26-04-2001	AU WO	7935100 A 0129009 A1		30-04-2001 26-04-2001
WO 9719065	A	29-05-1997	AU EP WO US US	7631496 A 0862560 A1 9719065 A1 6235746 B1 5958935 A		11-06-1997 09-09-1998 29-05-1997 22-05-2001 28-09-1999
WO 9509847	A	13-04-1995	AU AU CA WO EP JP US	693475 B2 7697694 A 2148931 A1 9509847 A1 0672035 A1 8503971 T 5612340 A		02-07-1998 01-05-1995 13-04-1995 13-04-1995 20-09-1995 30-04-1996 18-03-1997